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QUANTITATIVE STUDY OF THE EFFECTS OF MULTIPLE SUCCESSIVE CLOSED CEREBRAL LESIONS

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PREVIOUS quantitative studies of acute closed cerebral lesions produced by a hypothermal method showed a good correlation between symptoms and volumes of cerebral damage per hundred volumes of the brain in rabbits.[1] The average maximum quantity of damage permitting survival of 50 per cent of the animals was 14.3 volumes per hundred volumes of the brain. No animal survived with cerebral damage in excess of 18.5 per cent of the brain. Most animals with cerebral damage of these magnitudes recovered promptly from the anesthesia after production of lesions and then, after several hours of normal behavior, lapsed into an unconscious state which terminated in death. It seemed that factors which led to the delayed onset of symptoms were also restricting the amount of acute closed cerebral injury which could be produced without a fatal result. The purpose of the present study was to investigate these factors so that therapy of acute and subacute progressive cerebral damage might be analyzed in a quantitative way by experimental methods.

METHODS

Albino rabbits, 3 to 6 months of age and weighing 4 to 6 pounds (about 2 to 3 Kg.), were used.

The closed intracerebral hypothermal lesions were produced by a technic described elsewhere.[1] Briefly, this consisted of aseptic exposure of the calvarium at the vertex of the skull of an anesthetized animal and controlled freezing of the calvarium and underlying cerebrum with a special instrument. Lesion 1 was made in the left occipitoparietal region, care being taken to produce a sublethal lesion. The scalp was then closed with silk sutures. If the animal survived, the procedure was repeated after the lapse of a chosen interval of time. A second lesion (lesion 2) of sublethal volume was then produced in the right occipito-

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1. Taylor, C. B.; Hass, G. M., and Maloney, J. E.: Relations Between Volumes of Closed Hypothermal Cerebral Lesions and Symptoms in Rabbits, Arch. Path. **47**:450, 1949.

parietal region. Lesions 3, 4, 5 and 6 were then produced successively at the same intervals of time in the left parietal, right parietal, left frontal and right frontal regions, respectively. In most instances, animals failed to survive the complete series of lesions, so that the number of lesions varied from two to six.

There were four groups of animals. Successive cerebral lesions were produced at intervals of twenty-four hours in 12 rabbits, forty-eight hours in 12 rabbits, seventy-two hours in 4 rabbits and ninety-six hours in 4 rabbits. Repeated clinical observations were made, and a record was kept of the time of onset and the duration of paralysis, stupor, coma or convulsions, as well as the duration of life after production of the last lesion. Five types of clinical courses based on the variable responses of the animals were recognized.

If an animal lived for twenty-four hours after the production of a lesion, it was regarded as a survivor in accordance with previous experience.[1] Each experiment, therefore, was terminated either when the animal died of lethal lesions or was killed twenty-four hours after production of the final lesion.

The determination of the volumes of cerebral damage per hundred volumes of the brain was made by methods described elsewhere.[1] These involved measurement of the volume of the brain and the volume of each lesion. The ratio between the sum of the volumes of individual lesions and the total volume of the brain was taken as a standard approximation of the percentage volume of cerebral damage.

RESULTS

The characteristics of acute closed cerebral lesions produced by the hypothermal method have been described previously.[1] They were discrete circumscribed lesions characterized principally by necrosis, hemorrhage and edema of the cerebral cortex and underlying white matter. The necrosis affected all cerebral elements within the sharp boundaries of each lesion and was uniform in nature. There was no suppuration, and structure of connective tissues was well preserved. Hemorrhage was restricted to the region of injury. Free bleeding into the subarachnoid space was not encountered. Bleeding into the ventricles occurred only when lesions involved ventricular walls, but this complication was not encountered in the present study, because lesions of great depth were not produced. Edema was grossly apparent in the lesions and adjacent cerebral tissue.

The production of successive lesions spaced at intervals of several hours led to three complications which made evaluation of data more difficult than in the experiments previously reported. Reopening of surgical wounds of the scalp led to infection at times, but this did not seem to contribute to death of animals. The second complication was overlapping of adjacent lesions at their margins. Because of this, errors in the calculation of percentage volume of cerebral injury were greater than when lesions were separated from one another by normal brain. The third complication was the gradual decrease in size of lesions as they healed. This introduced an error in the determination of percentage volume of cerebral injury. The error was always in underestimating the actual percentage volume of damage.

Previous experience indicated that rabbits could tolerate less than 9.4 volumes of acute cerebral damage per hundred volumes of brain without symptoms. When the amount of cerebral damage was 9.4 to 18.5 per cent of the brain, symptoms, at times leading to death, occurred in many animals (see chart 1). The minimum volume that would lead to death of 50 per cent of the animals ($M.L.V._{50}$) was 14.3 per cent of the brain. All animals with acute closed cerebral injury in excess of 18.5 per cent died.

For these reasons, it was necessary to control the volume of acute injury at each successive stage of the experiment. Each acute lesion had to be small, so that the summation of effects of successive lesions would not be unduly obscured by the effect of the most recent acute lesion. The data in table 4 show the maximum, minimum and average percentage volumes of cerebral injury, as represented by single lesions. The maximum size of any single lesion in the series was 13.4 per cent of the brain. The average size of lesions was about 4 to 6 per cent. There was little difference among the dimensions of lesions in the four groups of animals with spacing of lesions at twenty-four, forty-eight, seventy-two and ninety-six hour intervals. It was concluded that the slight variability in size of lesions had little influence on differences in behavior of the four groups of animals.

The limits of survivable damage in the four groups of animals are shown in tables 1, 2 and 3. (See also chart 2.) When lesions were produced at intervals of twenty-four hours, the maximum survivable damage was 22.6 per cent. This was produced by three successive lesions. Attempts to exceed this value resulted in death of the animals. The remaining 11 animals in this group behaved in the same manner as animals with comparable injury produced by multiple simultaneous

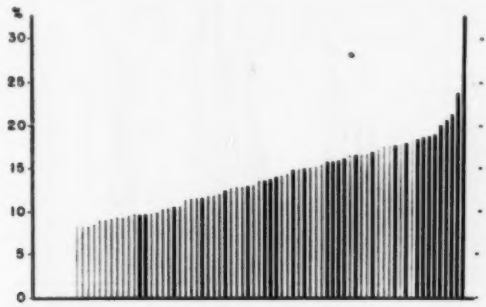

Chart 1.—Each bar represents an animal with acute unilateral or bilateral cerebral lesions produced at one operation. The height of the bar indicates the percentage volume of cerebral damage. Each interrupted bar represents an animal which survived and each solid bar an animal which died.

lesions.[1] Therefore, the spacing of successive lesions at intervals of twenty-four hours had about the same effect as if the lesions had all been produced at one time.

The production of successive cerebral lesions at intervals of forty-eight hours led to survival of 5 of 12 animals with 20.2 to 29.1 volumes of cerebral injury per hundred volumes of brain. This was a definite indication that successive lesions had less effect when the interval between lesions was forty-eight rather than twenty-four hours.

Three of 4 animals with lesions produced at intervals of seventy-two hours survived with 22.4, 23.6 and 25.9 volumes of cerebral injury, respectively, per hundred volumes of brain. Similarly, 4 of 4 animals with lesions produced at intervals of ninety-six hours survived with 20.9, 26.8, 27.5 and 29.2 volumes of cerebral injury, respectively, per hundred volumes of brain. These data indicate that although there was some advantage to the animal if lesions were produced at intervals greater than forty-eight hours, the advantage was not great in terms of either survival or recuperation of cerebral function.

The signs and symptoms which the animals showed after the production of each successive lesion were recorded. Five types of clinical courses were recognized. Type 1 was characterized by rapid recovery from the operation without subsequent symptoms; type 2, by a delayed recovery of consciousness in the immediate postoperative period without subsequent symptoms; type 3, by a normal or slightly delayed recovery of consciousness in the immediate postoperative period, followed by an asymptomatic return to normal behavior, then a lapse into stupor and coma with death before the twenty-fifth postoperative hour; type 4, by a lack of recovery of consciousness following the operation, with death occurring usually within two to four hours; type 5, by a persistent stupor or vegetative state, which usually continued for days without much change. The animals assumed a semireclining posture, moved about sluggishly on stimulation and did not eat well. No well defined motor paralysis was encountered in any of the five types of clinical courses.

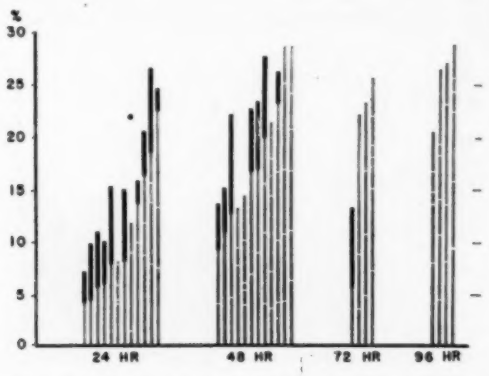

Chart 2.—The total height of each bar indicates the sum of successive percentage volumes of cerebral damage in an animal. Each bar is subdivided into columns which represent the individual volumes of each successive lesion. The interval of time between operations producing successive lesions is indicated at the base of each group of bars. When the final lesion resulted in death, the percentage volume of the brain occupied by the final lesion is indicated by the length of the terminal solid section of the bar.

Previous experience with acute unilateral or acute simultaneous bilateral lesions showed that there was good correlation between the type of clinical course and the percentage volume of cerebral damage. The type of clinical course was clearly established within twenty-four hours after the operation. No new signs or symptoms developed, thereafter, except in the animals which lost weight and strength during the prolonged stupor of the type 5 clinical course. In the acute experiments involving a single operation it was found that when the quantity of cerebral damage was less than 14.3 per cent of the brain, most animals followed clinical courses of type 1 and type 2. When the quantity of cerebral damage was about 14.3 per cent of the brain, most animals followed clinical courses of types 3, 4 and, in rare instances, 5. No animal survived when the cerebral damage was greater than 18.5 per cent of the brain.

The present experiments dealing with successive acute cerebral lesions produced at intervals of twenty-four hours gave the following relations between the percentage volume of cerebral damage and the type of clinical course. (See also table 1.)

Type 1: range of volume of cerebral damage 1.3 to 13.7 per cent; average, 7.2 per cent.

Type 2: range, 4.2 to 18.6 per cent; average, 10.6 per cent.

Type 3: range, 9.9 to 15.2 per cent; average, 12.4 per cent.

Type 4: range, 7.1 to 26.7 per cent; average, 19.1 per cent.

Type 5: range, 11.8 to 22.6 per cent; average, 15.3 per cent.

A comparison of these data and those reported previously shows that multiple lesions spaced at intervals of twenty-four hours led to essentially the same result

TABLE 1.—*Clinical Results of Increasing the Percentage Volume of Cerebral Damage by Producing Successive Cerebral Lesions at Intervals of Twenty-Four Hours**

Experiment Number	Percentage Volume of Brain Lesion 1 †	Percentage Volume of Brain Lesions 1 and 2	Percentage Volume of Brain Lesions 1 to 3	Percentage Volume of Brain Lesions 1 to 4	Percentage Volume of Brain Lesions 1 to 5
83	6.8 (1)	13.7 (1)	22.6 (5)	25.1 (4)	.....
1	8.0 (1)	14.1 (2)	18.6 (2)	26.7 (4)	.....
84	8.9 (1)	12.1 (5)	16.4 (5)	20.8 (4)	.....
10	10.2 (1)	13.8 (5)	16.0 (4)	.....	.....
14	9.1 (1)	11.8 (5)	.....	.....	.....
16	1.3 (1)	8.1 (1)	15.2 (3)	.....	.....
15	4.2 (1)	4.6 (1)	5.9 (1)	7.9 (1)	8.1 (1)
8	7.9 (1)	15.5 (3)	.....	.....	.....
85	6.0 (1)	10.1 (3)	.....	.....	.....
86	5.7 (2)	11.1 (3)	.....	.....	.....
17	4.4 (1)	9.9 (3)	.....	.....	.....
6	4.2 (2)	7.1 (4)	.....	.....	.....

* The types of clinical courses are indicated by numerals 1 to 5 in parentheses adjacent to the percentage volume of cerebral damage.

† In this and subsequent tables the percentage volume represents the ratio between the total volume of the lesions and the volume of the brain.

as similar lesions produced simultaneously, with the exception that multiple spaced lesions were more frequently followed by a type 5 clinical course. These animals always had a large total volume of cerebral damage in proportion to volume of brain.

When acute cerebral lesions were produced successively at intervals of forty-eight hours, the following correlations between type of clinical course and percentage volume of cerebral damage were obtained. (See table 2.)

Type 1: range, 3.8 to 17.2 per cent; average, 9.0 per cent.

Type 2: range, 11.0 to 25.5 per cent; average, 15.9 per cent.

Type 3: range, 13.9 to 29.0 per cent; average, 21.9 per cent.

Type 4: range, 23.0 to 28.2 per cent; average, 25.6 per cent.

Type 5: range, 14.7 to 29.1 per cent; average, 21.8 per cent.

These data show that the quantity of cerebral damage could, on the average, be increased about 40 to 50 per cent in representative surviving groups, such as type 2 and type 5, if lesions were spaced at intervals of forty-eight rather than

twenty-four hours. It is to be noted that as the volume of cerebral damage was progressively increased the animals tended to follow successively the clinical courses in the order type 1, type 2, type 5.

When multiple cerebral lesions were produced successively at intervals of seventy-two and ninety-six hours, the following correlations between clinical course and percentage volume of cerebral damage were obtained. (See also table 3.)

TABLE 2.—*Clinical Results of Increasing the Percentage Volume of Cerebral Damage by Producing Successive Cerebral Lesions at Intervals of Forty-Eight Hours**

Experiment Number	Percentage Volume of Brain Lesion 1	Percentage Volume of Brain Lesions 1 and 2	Percentage Volume of Brain Lesions 1 to 3	Percentage Volume of Brain Lesions 1 to 4	Percentage Volume of Brain Lesions 1 to 5	Percentage Volume of Brain Lesions 1 to 6
42	6.4 (1)	11.3 (2)	17.0 (1)	24.8 (5)	29.1 (5)	.....
43	4.5 (1)	11.0 (2)	17.3 (2)	25.5 (2)	29.0 (3)	.....
62	4.3 (1)	10.4 (1)	17.0 (2)	23.8 (5)	26.7 (3)	.....
60	3.8 (1)	7.3 (1)	14.7 (5)	18.3 (5)	21.7 (5)	21.9 (5)
67	4.2 (1)	11.0 (1)	15.9 (1)	20.2 (5)	28.2 (4)	.....
68	9.2 (1)	17.2 (1)	23.7 (3)	.....	.....	.....
61	7.0 (1)	16.9 (1)	23.0 (4)	.....	.....	.....
51	4.3 (1)	5.4 (1)	6.2 (1)	10.5 (1)	14.8 (5)	.....
30	7.9 (1)	9.8 (1)	13.4 (2)	.....	.....	.....
70	4.8 (1)	13.0 (1)	22.5 (3)	.....	.....	.....
59	11.2 (1)	15.5 (3)	.....	.....	.....	.....
21	4.4 (1)	9.3 (1)	13.9 (3)	.....	.....	.....

* The types of clinical courses are indicated by numerals 1 to 5 in parentheses adjacent to the percentage volume of cerebral damage.

TABLE 3.—*Clinical Results of Increasing the Percentage Volume of Cerebral Damage by Producing Successive Cerebral Lesions at Intervals of Seventy-Two Hours (Exper. 38, 20, 30, 37) and Ninety-Six Hours (Exper. 22, 41, 39, 40)**

Experiment Number	Percentage Volume of Brain Lesion 1	Percentage Volume of Brain Lesions 1 and 2	Percentage Volume of Brain Lesions 1 to 3	Percentage Volume of Brain Lesions 1 to 4	Percentage Volume of Brain Lesions 1 to 5	Percentage Volume of Brain Lesions 1 to 6
38	5.5 (1)	13.5 (3)	.....	.....	.....	.....
20	3.7 (1)	9.0 (1)	22.4 (5)	.....	.....	.....
30	5.0 (1)	10.9 (5)	16.7 (5)	23.6 (5)	.....	.....
37	7.3 (1)	15.2 (2)	18.2 (5)	19.6 (5)	22.3 (5)	25.9 (5)
22	8.1 (1)	13.5 (1)	15.1 (1)	16.9 (1)	20.9 (5)	.....
41	4.6 (1)	10.8 (1)	14.3 (1)	18.4 (1)	19.6 (1)	26.8 (1)
39	8.2 (1)	13.8 (1)	23.3 (5)	27.5 (5)	.....	.....
40	9.5 (1)	16.2 (1)	22.3 (5)	24.0 (5)	25.8 (5)	29.2 (5)

* The types of clinical courses are indicated by numerals 1 to 5 in parentheses adjacent to the percentage volume of cerebral damage.

Type 1: range, 3.7 to 26.8 per cent; average, 11.8 per cent.

Type 2: one animal, 15.2 per cent.

Type 3: one animal, 13.5 per cent.

Type 4: no animal.

Type 5: range, 10.9 to 29.2 per cent; average, 23.4 per cent.

These studies indicate that the quantity of cerebral damage could be still further increased with survival of the animal if lesions were spaced at intervals of seventy-two or ninety-six hours rather than forty-eight hours. The principal effect of the more prolonged spacing, however, was to increase the number of animals surviving with the type 1 or type 5 clinical course and to decrease the number of animals following the fatal type 3 and type 4 clinical courses. It was apparent that still further cerebral ablation could have been accomplished had we attempted to maintain the nutritional state of the animals as they lapsed into the semi-stuporous vegetative state of the type 5 clinical course. If it is desirable for experimental purposes to do extensive cortical ablation without opening the skull and with a minimum mortality, the interval between operations should be at least ninety-six hours.

COMMENT

Three variables were most important in governing relationships between the percentage volume of cerebral damage and the clinical manifestations of animals. These variables were: first, the percentage volume of acute cerebral damage; second, the percentage volume of cerebral damage due to previous injury and, third, the interval of time which elapsed between production of acute damage and preceding injury. When a minimum lethal volume of acute damage was produced at one operation, the animals usually soon recovered from the operation and after several hours of normal behavior lapsed secondarily into stupor and coma, terminated in a short time by convulsions and death. It was believed that the delayed onset of symptoms might be secondary to progressive pericapillary hemorrhage in the lesions, progressive edema in the area of cerebral degeneration or to the action of some toxic substance arising from disintegrating neural tissue. Postmortem studies failed to prove that the delayed onset of symptoms could be attributed to progressive pericapillary hemorrhage. Edema was apparent in and around the lesions, but measurement of the extent or the progression of this reaction was not possible. Even if it had been possible to measure accurately the increase of intracranial pressure, the measurements of pressure alone would not have distinguished between effects of edema and those of hemorrhage. No steps were taken to investigate the possible presence of a toxin liberated by the degenerating tissues.

It was believed that the role of edema might be more clearly defined if experiments could be done to take advantage of the fact that in the brain a hemorrhage continues to occupy space long after the edema which accompanies hemorrhage has subsided. For this reason, successive sublethal lesions were produced at intervals of twenty-four, forty-eight, seventy-two and ninety-six hours. These studies showed that when lesions were spaced at intervals of twenty-four hours, the mean survivable percentage volume of cerebral damage was not appreciably increased, so that the effect was the same as if the lesions had been produced simultaneously. However, when successive lesions were pro-

duced at intervals of forty-eight, seventy-two or ninety-six hours, the mean survivable percentage volume of total cerebral damage was greatly increased. The data indicated that a lapse of forty-eight hours after production of a near lethal volume of cerebral injury was sufficient to permit the reproduction of a second near lethal volume of cerebral injury without death. Increasing the interval of time from forty-eight to seventy-two or ninety-six hours seemed to have little additional effect. It was concluded that the factor responsible for this effect reached a maximum at about seven to ten hours after the production of an acute

TABLE 4.—*The Maximum, Minimum and Average Percentage Volume of the Brain Occupied by Lesions in the Six Different Cerebral Locations in the Four Groups of Experimental Animals with Multiple Lesions Spaced at Intervals of Twenty-Four, Forty-Eight, Seventy-Two and Ninety-Six Hours*

Interval of Time Between Lesions	Size of Lesions	Percentage Volume of Brain Lesion 1	Percentage Volume of Brain Lesion 2	Percentage Volume of Brain Lesion 3	Percentage Volume of Brain Lesion 4	Percentage Volume of Brain Lesion 5	Percentage Volume of Brain Lesion 6
24 hours.....	Maximum	10.2	7.6	8.9	8.1	...	...
	Minimum	1.3	0.2	1.3	2.0	...	...
	Average	6.4	5.4	4.6	4.5	...	...
48 hours.....	Maximum	11.2	9.9	9.5	8.2	8.0	0.2
	Minimum	3.8	1.1	0.8	3.6	3.4	0.2
	Average	6.0	5.5	5.6	5.8	4.7	0.2
72 hours.....	Maximum	7.3	8.0	13.4	6.9	2.7	3.6
	Minimum	3.7	5.3	3.0	1.4	2.7	3.6
	Average	5.4	6.8	7.4	4.1	2.7	3.6
96 hours.....	Maximum	9.5	6.7	9.5	4.2	4.0	7.2
	Minimum	4.6	5.4	1.6	1.7	1.2	3.4
	Average	7.6	6.0	5.2	3.0	2.3	5.3

lesion and that it persisted thereafter for at least twenty-four hours and disappeared rapidly in the interval between twenty-four and forty-eight hours. It is assumed, without complete proof, that the factor was probably congestion and edema in and around the lesion. At least, the curve of degree of influence of this factor in time has been established.

The percentage volume of cerebral damage due to previous injury influenced the clinical course of animals in other ways than by its contribution to the lethal effect of additional injury. This was apparent in animals of all groups. Increments of cerebral damage spaced at intervals of twenty-four hours led to the frequent appearance of a type 5 clinical course, which was rarely encountered in animals with a similar volume of cerebral damage produced at a single operation. This clinical course, characterized by semistupor and lack of ambition or desire to eat, was usually terminated by a small increment of cerebral damage

produced by the next operation. After the final operation the animals pursued the type 4 clinical course and died after several hours without a postoperative return of consciousness. This same trend of conversion from a type 1 or a type 2 to a type 5 clinical course was still more pronounced when increments of cerebral damage were spaced at intervals of forty-eight hours and most pronounced when the interval of time between operations was seventy-two or ninety-six hours. The onset and persistence of the type 5 clinical course seemed to be more closely correlated with progressive subacute cerebral degeneration and widespread cortical inactivation than with the actual percentage volume of cerebral damage, although most animals had a volume of cerebral injury in excess of that which an animal could survive at a single operation.

It may be permissible to compare the findings in the experimental animals with findings in human patients who have acute lesions of similar nature in the cerebrum or in intracranial neoplasms. Certain types of human cerebral infarction or cerebral hemorrhage of nontraumatic origin closely resemble the experimental lesions. As a rule human cerebral vascular accidents of the relative magnitude of the experimental lesions lead promptly to unconsciousness. Experimentally, this symptom was delayed in onset unless the percentage volume of acute cerebral damage was very large and essentially beyond limits of survival or unless the preexisting percentage volume of cerebral damage was sufficient to create a persistent semistuporous condition, represented by the type 5 clinical course. Furthermore, most people with lesions of the magnitude produced experimentally exhibit localizing neurologic signs. Localizing signs were not detected in the animals, nor were they expected, because the cortical areas and tracts concerned with motor function in rabbits are different anatomically from those in man. Most persons with lesions of the relative magnitude and location of the experimental lesions improve rather rapidly or die within twelve to seventy-two hours after the onset of symptoms. There was considerable similarity in this respect between the usual clinical course of patients and that of animals with sufficient cerebral damage to cause symptoms. We have found that when single or multiple simultaneous acute lesions were produced in a previously undamaged brain, the development of significant symptoms occurred either in the first few postoperative hours or not at all. If significant symptoms developed, death, with rare exceptions, occurred in twenty-four hours. However, if acute lesions were produced in a brain already damaged by previous lesions, there was a pronounced tendency for animals to remain semistuporous or comatose for several days . The course of these animals more closely resembled the lingering, prolonged comatose state of some

patients with cerebral infarction or hemorrhage. Some of these animals might have recovered had their nutritional needs been cared for sufficiently well, but they seemed to be in an irreversible vegetative state.

There is little need to discuss in detail the gross and microscopic similarities between many human lesions and those produced experimentally. Sudden focal cerebral necrosis with variable well restricted hemorrhage within the cerebrum and an accompanying edema within the area of necrosis and neighboring gray and white matter are conspicuous features of the human and experimental lesions. Resolution and repair, as previously described, are nearly identical in both processes. In our opinion, the similarities are sufficient to justify an attempt to establish by quantitative experimental methods a sound basis for treatment of pertinent types of acute expanding intracerebral lesions in man.

SUMMARY

Previous studies have shown that acute closed cerebral lesions characterized by edema, hemorrhage and necrosis could be reproduced quantitatively in rabbits by a standard hypothermal method. The average minimum lethal amount of cerebral damage was 14.3 volumes per hundred volumes of the brain, and no animal survived cerebral damage in excess of 18.5 per cent of the brain. The present experiments have shown that if acute cerebral lesions of sublethal dimensions were produced successively in the same animal at intervals of twenty-four hours, no increase in the average minimum lethal percentage volume or maximum survivable percentage volume of cerebral damage occurred. However, if acute cerebral lesions were produced successively in the same animal at intervals of forty-eight hours, the average minimum lethal percentage volume and maximum survivable percentage volume of cerebral damage were increased by about 40 to 50 per cent. When the interval between operations to produce successive lesions was prolonged to seventy-two or ninety-six hours, the results were about the same as those obtained when the interval was forty-eight hours. The survivable magnitude of cerebral ablation by these methods was about 50 per cent of the cerebrum or 30 per cent of the brain. These data indicated that factors responsible for death from acute cerebral injury of this type had not begun to subside until twenty-four hours had elapsed but had largely disappeared by the end of forty-eight hours. There were reasons for believing that cerebral edema was the most important of these factors.

Clinical observations indicated that most animals with an acute lethal lesion produced at a single operation had a period of several hours of normal postoperative behavior before the onset of stupor, coma and convulsions followed by death. When a similar or greater total volume

of cerebral damage was produced by acute lesions made successively at intervals of twenty-four, forty-eight, seventy-two or ninety-six hours, the animals showed a pronounced tendency to lapse into a stuporous irreversible vegetative state without localizing neurologic signs. This seemed to be related to a combination of progressive cerebral degeneration and total percentage volume of cerebral damage.

These observations, correlating symptomatic course with quantity, location and age of closed cerebral lesions, define experimental conditions which should prove useful in validation of therapy of acutely expanding intracerebral lesions characterized by edema, hemorrhage and necrosis.

INTESTINAL EMPHYSEMA IN INFANTS

A Review of the Literature, with Seventeen New Cases Reported

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INTESTINAL emphysema of infants (i. e., emphysema intestinorum, gas cysts of the intestine, diffuse emphysema of the intestinal wall, multiple cysts of the intestine), first described as a clinical entity by Bang,[1] in 1876, has been infrequently described in the literature. The term "pneumatosis cystoides intestini" has been used by some writers, and although not standard nomenclature it seems descriptive and inclusive. Jackson [2] collected 171 cases of this disease from the world literature and added one of his own in which an infant was involved, making a total of 12 cases in which the condition was observed in an infant. Lindsay and associates [3] described a case in detail in 1940. The apparent obscurity of this disease, coupled with the curious fact that 17 cases were observed during the period from January 1945 to September 1947 at the Children's Hospital, Washington, D. C., dictates the adding of these cases to the literature.

INCIDENCE AND PATHOGENESIS

The sporadic nature of the disorder has been noticed by others. An incidence of 4 cases in 260 autopsies, all occurring in one year, was noted by Moore.[4] Five of the 6 cases of Botsford and Krakower [5] were also observed within one year. Sex, race, climatic conditions, the season of the year and geography have not been shown to be definitely correlated with the incidence.

From the Department of Pathology, Children's Hospital.

1. Bang, B. L. F.: Nord med. ark. **8**:18, 1876.
2. Jackson, J. A.: Surg., Gynec. & Obst. **71**:675, 1940.
3. Lindsay, J. V.; Rice, E. C., and Selinger, M. A.: Arch. Path. **30**:1085, 1940.
4. Moore, R. A.: Am. J. Dis. Child. **38**:818, 1929.
5. Botsford, T. W., and Krakower, C.: J. Pediat. **13**:185, 1938.

The cause is obscure, investigation having failed to establish a definite etiologic factor. The coexistence of other diseases, notably colitis, ulcer, gastric carcinoma, appendicitis, strangulated hernia and parasitic infections, has been noted. Primary pneumatosis can occur, but most commonly it is secondary, associated with a basic gastrointestinal disorder.

Various theories have been advanced, with (1) the bacterial and (2) the mechanical the most prominent. In addition Menna [6] postulated (3) neoplasm, (4) hematoma, (5) local change in fat metabolism and (6) parasitosis as causal conditions. The bacterial theory subscribes in part to the idea that bacterial action produces gas in the tissues of the wall of the intestine. No conclusive bacteriologic studies have been reported, although various authors have described bacteria observed in the cysts or their vicinity either of a specific nature or of the variety normally found in the intestine. The latter are thought to invade the lymphatic channels under certain conditions. The clinical picture is not one of a gas-forming infection, and the gas recovered from the cysts contains mostly oxygen, which is not in keeping with bacterial infections.

The mechanical theory states that an increase in the intraluminal pressure occurs, with a break in the mucosa. The latter is due to gaseous overdistention or localized infection of the mucosa. With hyperperistalsis or obstruction the gas is forced through the defective mucosa and accumulates in the various layers and beneath the serosa. It may often spread through the lymphatic channels or along the peritoneal planes. Various authors have expressed the belief that the gas is disseminated into the tissues rather than that it spreads exclusively by way of lymphatic channels.

CLINICAL FINDINGS

The patients do not exhibit symptoms which can be directly referred to pneumatosis, and the diagnosis is made usually after death. The infants are in poor general condition. Some observers, notably von Hacker [7] and Coelho,[8] described the sensation of crepitation on palpation of the abdomen, with a peculiar tympanism on percussion. The abdomen is usually soft and compressible. The distended bowel loops may feel like tumor masses, although the size varies from day to day. These signs vary with the location of the gas and the extent of involvement. The symptoms of gastritis, ulcer, stenosis, etc., all normally overshadow signs of pneumatosis. Fever and symptoms of an infection of the respiratory tract are common.

6. Menna, L.: Policlinico (sez. chir.) **47**:220, 1940.
7. von Hacker, cited by Memmi, R.: Policlinico (sez. chir.) **141**:408, 1934.
8. Coelho, N. A.: Ann. Fac. de med. de São Paulo **15**:201, 1939.

European literature, and recently American reports, have contained descriptions of the roentgen aid to diagnosis. Matranola [9] described a typical roentgenogram, which he considered pathognomonic, accompanied by symptoms of pyloric stenosis. Learner and Gazin [10] stated that translucent areas of gas are seen in the contour of an otherwise normal bowel and that when a contrast medium is used there is an inability to fill the lumen, giving the impression of filling defects. Areas of decreased density are observed between the contrast material and the outer intestinal wall. The presence of this inconsistent filling defect of increased translucency is considered pathognomonic by Learner.

CASES OBSERVED

During the period from January 1945 to September 1947, at the Children's Hospital, as stated, 17 infants under 8 months of age were shown at autopsy to have intestinal emphysema (table). Five hundred and one autopsies were performed within the same period. Ten of

Statistical Information

Year	Cases	Male	Female	White	Negro	Age, Months				
						1	2	4	6	8
1945.....	10	5	5	7	3	3	4	1	1	1
1946.....	5	3	2	2	3	2	0	2	1	0
1947.....	2	2	0	2	0	1	1	0	0	0
Total....	17	10	7	11	6	6	5	3	2	1

the infants died in 1945, 5 in 1946 and 2 in the first nine months of 1947. No cases of the disease have been seen since that time. Eleven of the infants were white and 6 were Negro. Ten were males and 7 were females. Nine (54 per cent) of the patients were observed in the months of March and April.

It is evident from the various theories that the pathogenesis is uncertain. The mechanical theory seems most likely, although attempts to produce pneumatosis experimentally by injecting air into the peritoneal lymphatic vessels have been unsuccessful. For pathologic changes to be present, ulcerative gastrointestinal lesions occurring concomitantly seem to be necessary. Thirteen of our 17 patients had ulcerative ileocolitis, while the remaining 4 had various stages of ileocolitis. While a basic bacterial factor appeared to be combined with mechanical factors in many instances, bacterial cultures, both ante mortem and post mortem, were not significant. Diarrhea was present in a majority of the cases, but except for the recovery of Salmonella in 2 instances bacterial

9. Matranola, cited by Memmi, R.: Policlinico (sez. chir.) **141**:408, 1934.

10. Learner, H. H., and Gazin, A.: Am. J. Roentgenol. **56**:464, 1946.

data were insignificant. The cause of pneumatosis of the intestines probably is a combination of the two types of factors with which the major theories are concerned.

All of our patients had temperatures ranging up to 105 F. Fifteen had infection of the respiratory tract during some stage of their illness. The 2 remaining children had severe infectious diarrhea.

Photomicrograph showing cystic spaces in the submucosa and muscularis of the colon; × 50.

Vomiting and diarrhea were prominent. All but 2 patients showed a loss of weight during the period of hospitalization.

Despite the awareness of the existence of this disease, none of the clinical signs described by others were definitely ascertained to be present in these cases. In 1 case the diagnosis was substantially championed before death, but in that case the infant, moribund, was seen late in the

year 1945, when circumstantial evidence pointing to the diagnosis was most prominent. Clinical impressions failed to warrant the taking of roentgenograms in our cases. Usually the basic pathologic observations caused attention to be diverted into other channels.

THE LESIONS

The lesions described in the literature had a predilection for the distal part of the ileum, with the cecum, ascending colon and jejunum, in that order, most frequently involved.[11] Rarely the stomach, the omentum and the gastrohepatic ligament have been involved. In our series the ileum was involved in 12 cases, the cecum in 10, the ascending colon in 7, the jejunum in 5, the transverse colon in 2 and the descending colon and the mesentery of the upper part of the ileum in 1. Masson [12] previously stated that the transverse and descending portions of the colon are spared. Grossly, the intestinal wall is found to be involved with air-containing cysts varying from pinpoint size to pea size. Rarely they may be larger. The cysts are noted in all layers of the intestines. When situated beneath the serosa the affected segment of the intestine shows multiple cysts. In gross appearance the intestine involved is like "sponge rubber."

Microscopically, the cystlike spaces contain gas and occasionally a protein-like material. There is no obvious endothelial lining, and the spaces resemble ruptured lymph spaces. There are varying degrees of inflammatory changes with hemorrhage, thrombus formation in the smaller blood vessels and edema (figure). Moore [4] noted that in children the predominant location of the cysts was in the mucosa and submucosa, in contradistinction to adults, in whom the serosa was most commonly involved. He found giant cells infrequently and only with smaller cysts in association with fibrosis and fibrin deposits.

COMMENT

The condition described here actually has minor clinical significance. The sporadic occurrence has little correlation with race, sex, season or geography, although it is interesting that cases are observed almost always in groups. The condition probably has been recognized more often than has been reported and when noted has been regarded as insignificant by the observers. It seems probable that the increased use of sulfonamides and antibiotics, along with the lowered incidence and lessened severity of infections of the gastrointestinal and respiratory tracts, has decreased the incidence of pneumatosis cystoides intestini.

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11. Urban, H.: Forschr. a. d. Geb. d. Röntgenstrahlen **55**:231, 1937. Bang.[1] Jackson.[2] Lindsay and others.[3] Moore.[4] Botsford and Krakower.[5] Menna.[6] von Hacker.[7] Coelho.[8] Matranola.[10]

12. Masson, P.: Ann. d'anat. path. **2**:541, 1925.

The pathogenesis is probably described best by a combination of the two major theories stated. It is our belief that the condition is always associated with an alteration in the mucosa allowing entrance of bacteria and gas, aided by peristalsis and/or spasm of the intestine. The bacteria after entering the wall of the intestine may produce gas in some instances. The gas then penetrates the breaks in the mucosa traversing the lymphatic channels and extends directly along tissue planes.

The most common bacteria obtained by culturing rectal material before death and material from the lesions after death are of species not likely to cause the type of tissue destruction noted in pneumatosis. Pathogenic organisms, notably hemolytic Staphylococcus albus, were recovered in 3 cases and Salmonella enteritidis in 2. Although severe ulcerative ileocolitis is not uncommon in the patients, similar ulcerative lesions occur commonly unassociated with pneumatosis. Definite proof of the duration of pneumatosis cannot be given, but the pathologic alterations seem older than a few hours and are not due to postmortem changes.

SUMMARY

The infrequent, sporadic condition, emphysema of the intestine, is discussed. The pathogenesis is obscure and a combination of the two major theories, bacterial and mechanical, is advanced as depicting the probable cause.

Clinical and roentgen examination appear to be of little value in making a diagnosis, and a definite diagnosis is usually made only at necropsy.

The typical gross appearance of the involved intestine is that of "sponge rubber," and the microscopic picture is that of gas cysts of the intestinal wall.

Seventeen new cases are presented, which, with those previously reported, bring the total number of reported cases to 30.

A brief review of the literature is included.

NORTH AMERICAN BLASTOMYCOSIS

Report of a Case in Which a Patient with Meningeal Involvement was Treated with Streptomycin and Promin®

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NORTH American blastomycosis is a chronic specific fungous disease caused by Blastomyces dermatitidis. Two clinical forms are recognized, cutaneous and systemic. The cutaneous form typically is manifested by a solitary chronic or subacute ulcerating lesion, and secondary systemic involvement is rare. Systemic blastomycosis frequently involves the skin secondarily, and often the patient has widespread involvement of many internal organs. The lung is a focus in approximately 96 per cent of the cases, and the spleen, liver, bones, prostate and central nervous system may show involvement.

Involvement of the central nervous system is rare, as indicated by the fact that in 1939 Martin and Smith [1] were able to find only 16 acceptable cases reported in the literature. Although intracranial lesions are more common, occasionally the spinal cord may be attacked.[2] Meningeal involvement is most uncommon. In a review of the literature to 1945, Friedman and Signorelli [3] found less than 10 acceptable cases. Our review of the English literature has revealed 4 additional acceptable reported cases.[4]

Although a presumptive diagnosis of blastomycosis can be made on the basis of the clinical picture, it is necessary to resort to laboratory tests to make an unequivocal diagnosis. The organism must be identified in a direct smear of material from the available lesion; it must be grown on suitable culture mediums, and tissue sections must show

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From the Laboratory Service, Veterans Administration Medical Teaching Group, Kennedy Hospital.

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1. Martin, D. S., and Smith, D. T.: Am. Rev. Tuberc. **39**:375, 1939.

2. (*a*) Stober, A. M.: Arch. Int. Med. **3**:509, 1914. (*b*) Wade, W. H., and Bel, G. S.: ibid. **18**:103, 1916.

3. Friedman, L. T., and Signorelli, J. J.: Ann. Int. Med. **24**:385, 1946.

4. (*a*) Gáspár, I.: Arch. Neurol. & Psychiat. **22**:475, 1929. (*b*) Littman, M. L.; Wicker, E. H., and Warren, A. W.: Am. J. Path. **24**:339, 1948. (*c*) MacBride, C. M., and Thompson, E. I.: Arch. Dermat. & Syph. **27**:49, 1933. (*d*) Wilhelmj, C. M.: Am. J. M. Sc. **169**:712, 1925.

the characteristic histopathologic appearances.[3] Baker[5] expressed the belief that a biopsy specimen showing the characteristic tissue is sufficient for absolute diagnosis. He has described in detail the histopathologic observations characterizing blastomycotic infection. The lesions are essentially the same, regardless of the organ in which they occur. The typical lesion consists of miliary abscesses and granulomatous tissue containing blastomycetes, polymorphonuclear granulocytes (predominantly neutrophils), plasma cells, epithelioid cells, giant cells and necrotic debris. The presence of miliary abscesses and the predominance of polymorphonuclear cells, within these abscesses, help to differentiate blastomycosis from tuberculosis even in the absence of demonstrable specific organisms. In bone the lesion starts in the epiphysial region and is exceedingly destructive.[2a] Lesions of the skin show, in addition, marked epithelial hyperplasia, so that occasionally the lesion may be confused with epidermoid carcinoma.[3] However, the microscopic intraepidermal abscesses which are usually present in blastomycosis aid in differentiating the two conditions.

Treatment of the systemic form of infection by the classic means of roentgen rays, iodides and desensitization has been generally unsuccessful. Herrell and associates[6] and Meyer and Ordal[7] have found penicillin ineffective. Following is the report of a case in which streptomycin and promin® (sodium-p,p′-diaminodiphenylsulfone-N,N′-didextrose sulfonate) failed to alter the course of the infection.

REPORT OF CASE

A 55 year old Negro man was admitted to the Veterans Administration Hospital, Jan. 1, 1948, with a diagnosis of chronic suppuration of the lower lobe of the right lung and secondary anemia. There was a history of an acute onset of illness in July 1947, with distress in the right upper quadrant of the abdomen, vomiting and high fever. These symptoms persisted until the patient was admitted to a hospital Oct. 1, 1947, where a seven day course of penicillin was given. During the subsequent three months, he had episodes of fever, the temperature varying from 99 to 102 F., and occasionally brought up bloody sputum, although at this time he had no pain, chills or foul expectoration. He stated that he had lost 40 pounds (18 Kg.) during the two months prior to admission to the Veterans Administration Hospital.

On examination the patient was seen to be a well developed, well nourished Negro man, not appearing acutely ill. Positive findings were moderate guarding of the muscle and tenderness in the right upper quadrant of the abdomen and two small papular eruptions of the skin of the face. Examination of the lungs disclosed no abnormal condition.

On admission the blood count showed 3,800,000 red blood cells and 17,500 white cells per cubic millimeter. The hemoglobin content was 11.1 Gm. per

5. Baker, R. D.: Am. J. Path. **18**:479, 1942; Arch. Path. **44**:459, 1947.

6. Herrell, W. E.; Nichols, D. R., and Heidman, D. H.: J. A. M. A. **125**:1003, 1944.

7. Meyer, E., and Ordal, Z. J.: J. Infect. Dis. **79**:199, 1946.

hundred cubic centimeters. The differential white cell count showed neutrophils 76, lymphocytes 22, monocytes 1 and eosinophils 1 per cent. The sedimentation rate was 32 mm. per hour. Urinalysis gave results within normal limits. No parasites or ova were found in the stool specimens. Repeated examinations of sputum and gastric washings showed no acid-fast organisms with the exception of one report of a very rare acid-fast bacillus on direct smear. All cultures were negative for tubercle bacilli. Roentgen examination of the chest, Jan. 2, 1948, revealed, in the lower lobe of the right lung, an inflammatory process approximately 7 by 7 cm. A second roentgenogram, February 2, revealed in addition a bilateral infiltrative process suggestive of pulmonary edema.

Because of the roentgen findings and the one questionable positive result of an examination of sputum, tuberculosis was suspected. January 10, signs of minimal meningismus and occipital headache developed. Kernig's sign could be elicited, and a temperature of 103 F. was recorded. On repeated spinal taps the pressure of the spinal fluid varied from 100 to 560 mm. of water. The fluid was constantly cloudy. The white blood cell count varied from 719 to 1,266 per cubic millimeter, 51 to 91 per cent being polymorphonuclear neutrophils. Total proteins were elevated, while the sugar and the chlorides were at normal levels. The test for globulin was positive and the Kolmer test negative.

Because of the probability that the patient had tuberculous meningitis, on Jan. 10 treatment was begun, consisting of streptomycin, 2 Gm., intramuscularly, and promin,* 4 Gm., intravenously, daily and penicillin, 15,000 units, with streptomycin, 0.05 Gm., intrathecally, every two days. After one week of this regimen the patient's condition had not improved. By January 24 he had episodes of stupor and disorientation. At this time he was given sulfadiazine, 0.75 Gm. every four hours, and sulfamerazine, 0.75 Gm. every eight hours. No improvement occurred. February 5 the sulfonamides were supplanted by penicillin, 10,000,000 units daily for three days. The patient became quite stuporous and completely disoriented, and on February 18 all specific therapy was discontinued.

February 19, a smear of material from the small papillomatous lesion over the dorsum of the nose revealed a budding fungus characteristic of Blastomyces dermatitidis. A skin test for blastomycosis was negative. Potassium iodide therapy was begun. February 23, the patient's temperature rose to 104 F., his pulse rate to 105 per minute and respirations to 60 per minute, and the patient died.

At necropsy, three hours after death, the pertinent findings were confined to the lungs, the meninges and a small lesion of the bridge of the nose.

The left and right lungs weighed 710 Gm. and 630 Gm., respectively. Their surfaces were smooth and glistening, and the entire lung parenchyma had reduced crepitancy and finely nodular consistency. On section, the primary, secondary and tertiary bronchi were partially filled with a frothy reddish fluid, and a similar fluid exuded from the cut surface. No nodules could be seen on the cut surface.

The brain weighed 1,320 Gm., and the gyri were moderately flattened. All the structures about the base of the brain, from the optic chiasma posteriorly to the posterior part of the pons and including the cerebellar tonsils, were covered by yellowish gray granulomatous plaques, 2 to 4 mm. in thickness. Serial section of the brain revealed moderate bilateral symmetric dilatation of the lateral ventricles and a dilated cavum of the septum pellucidum. The third and fourth ventricles were also dilated. This internal hydrocephalus was the result of the fibrous adhesions and the granulation tissue which were abundant in the region of the foramens of Magendie and Luschka. The cut surface of the brain showed congestion of small blood vessels, most marked in the region of the pons.

The lesion over the dorsum of the nose was circular and measured 1 cm. in diameter. It was covered by a dry scale, and its borders were not raised.

On histologic examination the parenchyma of the lung showed many foci of granulomatous reaction, which varied from 0.5 to 2 mm. in diameter. These foci showed necrosis and suppuration and consisted of polymorphonuclear cells,

Fig. 1.—A granulomatous exudate extends from just anterior to the optic chiasma caudad over the cervical cord.

necrotic debris, epithelial cells, fibrous connective tissue and an occasional large multinucleated foreign body giant cell. Occasional round or oval yeastlike bodies 10 to 15 microns in diameter and with double-contoured, highly refractile walls were seen, and these were particularly prominent within the giant cells. The alveolar structure of the lung was intact except where replaced by these granulomatous lesions. Within the lumens of the alveoli considerable edema

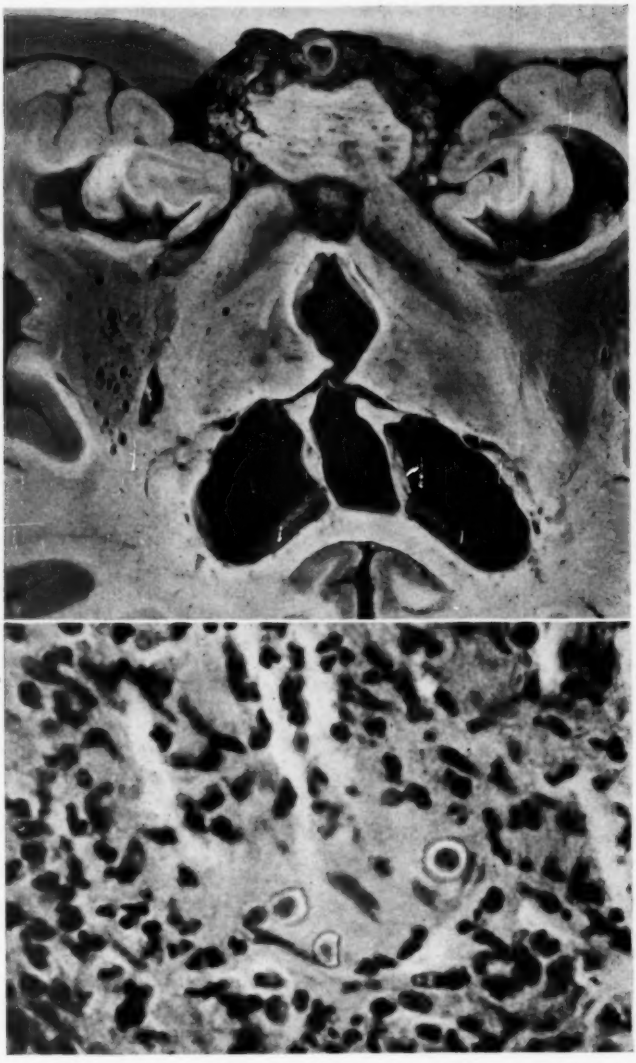

Fig. 2.—Upper part: There are infiltration and thickening of the meninges by granulomatous tissue over the pons. The lateral and third ventricles are dilated, and there is splitting of the septum pellucidum due to dilation of the cavum.

Lower part: Granulation tissue from the meninges. Note three organisms in the center of the section, one of which is just separating by budding. × 450.

fluid was present. As to the brain, except for congestion of small blood vessels, representative sections revealed no changes. The granulation tissue, previously mentioned, was closely adherent to the surface of the organ but did not extend into it. Here a granulomatous reaction was present, similar to that observed in the lung, although there were more miliary abscesses, giant cells and organisms than in the pulmonary lesions. Sections from the meninges showed more organisms to be forming buds than did sections from the lungs. A smear of material from the lesion of the nose revealed blastomycotic organisms, and smears and cultures of material from the lungs and meninges confirmed the diagnosis of blastomycosis.

COMMENT

The marked involvement of the lungs and the meninges places this case in the group of cases of systemic blastomycosis. The small superficial cutaneous lesion, in all probability, is merely another focus of the systemic disease. This lesion developed late in the course of the disease and neither was as extensive as, nor had the clinical appearance of, the lesions seen in cases of the cutaneous form of blastomycosis.

There are several possible sources for the meningeal involvement. One is the primary pulmonary focus, with a hematogenous spread. A second is the lesion of the bridge of the nose, with the infection extending to the meninges by lymphatic and venous return. Which of these mechanisms was responsible for the meningeal involvement in this instance could not be determined. Friedman and Signorelli [8] in reporting a similar case pointed out that if one accepts the premise of a hematogenous spread it would be difficult to explain why the meninges, which are infrequently involved, should be attacked while other organs and tissue which are more frequently involved should be spared.

Wilhelmj [4d] described a primary meningeal form of systemic blastomycosis, in which the meninges alone show involvement. He suggested that in this form the meninges are infected during the initial period of invasion and death occurs before the general metastatic foci appear. The portal of entry, presumably, would be pulmonary.

The therapeutic failure of penicillin and streptomycin is consistent with the findings in previous investigations.[8] However, this probably represents the first clinical trial of streptomycin and promin® in systemic blastomycosis.

SUMMARY

The literature of systemic blastomycosis with meningeal involvement is reviewed, and an additional case, in which the patient was unsuccessfully treated with streptomycin and promin,® is reported in detail.

8. Herrell and others.[6] Meyer and Ordal.[7] Stober.[2a]

FIBROSARCOMA OF THE HELIX OF THE EAR

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SARCOMA of the external ear is rare. Hand and O'Connor [1] in 1938 recorded a myxofibrosarcoma of the ear of a 5 year old girl. They found that only 2 cases of fibrosarcoma of the external ear had been reported in the preceding decade: one by Treer and Kálló,[2] the other by Speziale.[3] No additional reports have since appeared. In this paper 2 recently observed cases of fibrosarcoma of the helix are presented.

REPORT OF CASES

CASE 1.—J. D., a 71 year old white man, was first seen at the University of Oklahoma Hospitals Dec. 18, 1946. He stated that two months previously a small, nontender nodule appeared on the anterior and superior surface of the left ear. This progressively enlarged. A biopsy of the lesion made in the outpatient department revealed a cancer. He was admitted to the hospital December 31. Examination revealed a round purple mass, 3 cm. in diameter, pedunculated, soft, on the anterior superior surface of the left auricle. The site of the excision of biopsy tissue was not healed. The growth appeared not to involve the subjacent cartilage. The regional lymph nodes were not palpably enlarged. There were no other pertinent findings. Resection of most of the left auricle was performed by Dr. Harrell C. Dodson Jr. on Jan. 3, 1947. There was no evidence of recurrence of the growth when the patient was seen Dec. 6, 1948.

The specimen consisted of the upper two thirds of the left auricle. On the upper anterior portion of the helix was a soft mass 2.5 cm. in diameter, partly covered by a black crust. The growth was composed of homogeneous soft yellow-white tissue, involving only the soft parts and not extending to or invading the cartilage. Microscopic preparations (fig. 1) stained with hematoxylin and eosin revealed round, oval and cigar-shaped nuclei in a hardly discernible cytoplasm that faded into a delicate fibrillar ground substance. The cells were arranged in streams and whorls, in places closely packed, elsewhere farther apart. There was marked variation in the size and the shape of the cells; occasional cells had giant proportions, and many were seen in a state of division. Large, thin-walled

From the Department of Pathology, University of Oklahoma School of Medicine, and the University of Oklahoma Hospitals.

1. Hand, F., and O'Connor, G. B.: Ann. Otol., Rhin. & Laryng. **47**:1096, 1938.

2. Treer, J., and Kálló, A.: Orvosi hetil. **72**:1128, 1928.

3. Speziale, V.: Arch. ital. di otol. **43**:526, 1932.

blood spaces were numerous. There were occasional small areas of hemorrhage and necrosis. The growth extended to the covering epithelium, in places leaving it intact.

Case 2.—A. B., a 92 ear old white man, was admitted Sept. 1, 1948. He stated that two months previously, following trauma, a small, nontender mass appeared on the superior surface of the auricle of the right ear. The mass gradually enlarged. About two weeks before admission, a small portion of skin over the growth became ulcerated. Examination revealed a mass 2.5 cm. in diameter, covered with a yellow-brown crust and elevated 2 cm. above the cutaneous surface of the helix of the right ear. The growth was not movable over the

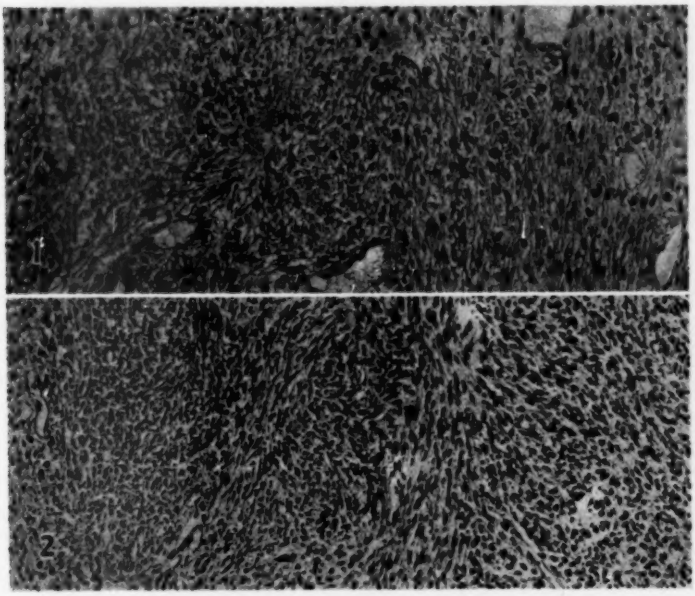

Fig. 1.—Microscopic structure of the growth in case 1; × 100.
Fig. 2.—Microscopic structure of the growth in case 2; × 100.

underlying cartilage. The regional lymph nodes were not palpably enlarged. There were no other pertinent findings. Resection of the upper third of the auricle of the right ear was performed by Dr. John H. Clymer September 7. The operative wound was well healed when the patient was last seen October 14.

The specimen consisted of the upper third of the right auricle. On the superior posterior surface of the helix was a firm gray-red mass, 3 by 2 by 2 cm. Most of the surface of the mass was crusted. The cut surfaces were light gray and had a fish meat appearance. The growth did not involve the cartilage. Microscopic preparations (fig. 2) stained with hematoxylin and eosin disclosed neoplastic cells with round or elongated, spindle-shaped nuclei in a stream and whorl-like

arrangement within a barely discernible cytoplasm fading into a delicate fibrillar ground substance. In places there were giant cell nuclei. Many cells were seen in a state of division. Within the fibrillar ground substance there were thin-walled blood vessels. Occasional areas of hemorrhage and necrosis were seen.

COMMENT

Fibroblasts readily multiply to provide the stroma for neoplasms of epithelial origin. Yet pure fibroma [4] and fibrosarcoma are uncommon. Fibrosarcoma, like other cancerous growths, seems to have sites of predilection.[5] Most commonly it arises from the connective tissue of mesenchymal organs rather than from that of the tunica propria of entodermal organs or from that of the corium of the skin. The anlage origin of fibrosarcoma as a component of Wilms's tumor and as a fibrosarcoma of the epididymis of a child is clear.[6] For fibrosarcoma as a part of carcinosarcoma of the mammary gland, another explanation has been offered: namely, that the epithelial element, the carcinoma, was dominant and that the connective tissue element, the sarcoma, was subservient and formed the stroma.[7] Neither of these factors appears to be involved in the development of the ordinary fibrosarcoma, nor in that of the growth occurring at the unusual site immediately beneath the skin in the helix of the ear. Both of our patients were past the seventh decade of life. Were it not that the patient whose myxofibrosarcoma was reported by Hand and O'Connor was 5, and the patient of Speziale 48, far advanced age might be considered as a predisposing factor. Since fibrosarcoma for some time remains localized and spreads by direct extension rather than by metastasizing through blood channels, cure may be effected by its early and complete removal.

SUMMARY

Fibrosarcoma of the helix of the ear is recorded as observed in a man aged 72 and in another aged 92 years.

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4. Halpert, B., and Dial, D. L.: Am. J. Path. **9**:905, 1933. Lingenfelter, F. M.; Clymer, J. H., and Halpert, B.: Surgery **25**:617, 1949.
5. Stout, A. P.: Cancer **1**:30, 1948.
6. Halpert, B., and Thompson, W. V.: Arch. Path. **43**:358, 1947.
7. Halpert, B., and Young, M. O.: Surgery **23**:289, 1948.

CONGENITAL ADENOMATOID MALFORMATION OF ONE LOBE OF A LUNG WITH GENERAL ANASARCA

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AND
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CONGENITAL adenomatoid malformation of the lung, usually involving one lobe or one lung, is a rare condition. In all the reported cases it occurred in a premature infant, stillborn in many instances, and was almost constantly associated with general anasarca of the infant and frequently also with hydramnios of the mother. Störk [1] reported a case in 1897, and since then 9 more cases have been recorded as far as we have been able to ascertain from the *Quarterly Cumulative Index Medicus* and individual reports.[2] Our case is the eleventh. The rarity of the condition justifies this report, which happens to be the first in the English language, the previous reports being in German.

REPORT OF A CASE

The mother, aged 30 years, was admitted to the obstetric service of the Railway Hospital, July 7, 1947, with amenorrhea, present for six months, and abdominal overdistention, present for one month. The course of pregnancy had been otherwise smooth until the last two weeks, when edema of the lower limbs was noticed. Fetal movements had been absent for a week. The patient had had four full term deliveries and one eight month premature labor. There was no history of acute hydramnios or anasarca of the fetus. She was an emaciated and pale woman with the abdomen markedly distended (96 cm. in circumference) and the uterus enlarged to 3 fingerbreadths below the xiphoid process, as if near term. There was pitting edema over the external genitalia, the suprapubic region and the lower extremities. The fetus was in breech presentation; the fetal heart was not

From the Department of Pathology, National Peking University College of Medicine.

1. Störk, O.: Wien. klin. Wchnschr. **10**:25, 1897.

2. (*a*) von Graff, E.: München. med. Wchnschr. **52**:598, 1905. (*b*) Lahm: Zentralbl. f. Gynäk. **43**:424, 1919. (*c*) Seyffert, M.: Arch. f. Gynäk. **112**:413, 1920. (*d*) Sternberg, C.: Verhandl. d. deutsch. path. Gesellsch. **19**:322, 1923. (*e*) Meyer, R.: Zentralbl. f. Gynäk. **48**:356, 1924; Ztschr. f. Geburtsh. u. Gynäk. **87**:658, 1924. (*f*) Wermbter, F.: Virchows Arch. f. path. Anat. **225**:26, 1925. (*g*) Nordmann, G.: Zentralbl. f. Gynäk. **50**:2945, 1926. (*h*) Esch, V. P.: Arch. f. Gynäk. **133**:32, 1928. (*i*) Koboth, I.: Frankfurt, Ztschr. f. Path. **50**:10, 1936.

heard. The Wassermann reaction of the blood was strongly positive. Induction of labor was started on the day after admission, and a dead girl was delivered on the third day, after passage of 3.5 liters of amniotic fluid. The Wassermann test of the amniotic fluid and of the cord blood was negative.

The fetus measured 35.5 cm. in length and weighed 1,080 Gm. The whole body, especially the face and the upper extremities, showed marked pitting edema. The abdominal cavity contained 20 cc. of clear yellowish fluid. The peritoneal surfaces were smooth and glistening. The left side of the diaphragm protruded below the costal margin, while the right dome was at the level of the fifth rib.

Fig. 1.—Tumor of the lower lobe of the left lung, the upper lobe, the heart and the aorta, and the right lung, viewed from behind. The upper lobe of the left lung has been displaced backward and downward.

The left thoracic cavity was occupied by a mass which pushed the diaphragm downward and displaced the mediastinum to the right side. Owing to cardiac displacement, the venae cavae were compressed. The mass represented the malformed lower lobe of the left lung. The lower branch of the left bronchus led into the mass for a short distance. The mass measured 8.5 cm. longitudinally, 6 cm. transversely and 4 cm. anteroposteriorly. It had many congested blood vessels under its pleural surface and was rather soft in consistency. Its cut surface presented a solid, grayish white tissue with many cysts of various sizes and shapes. Cysts scattered throughout the mass varied from 2 mm. to 1.5 cm. in

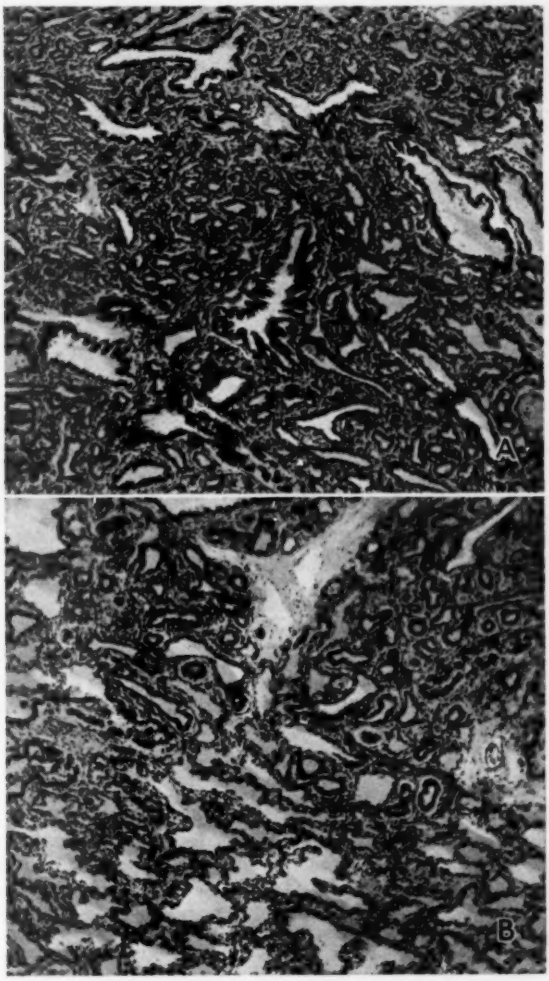

Fig. 2.—*A*, tumor showing large tubules (bronchioles) lined by pseudostratified columnar cells, similar to those of normal bronchiolar mucosa, and small tubules (terminal bronchioles) lined by cuboidal cells. These two types of tubules make up the bulk of the tumor. The overgrowth of the bronchioles, especially of the terminal bronchioles, is obvious, and the tumor may be regarded as a hamartoma. × 85.

B, peripheral portion of the malformed lower lobe of the left lung, showing malformed tissue or hamartoma in the upper half of the field and normal lung tissue in the lower half. × 85.

diameter. The largest was 4.5 cm. in its longest diameter. The cysts did not communicate with the left lower bronchus, but frequently with one another through small circular channels. The right lung was displaced, compressed and atelectatic, and congested. A small amount of clear yellowish fluid was in the left pleural cavity; none, in the right cavity. The other organs showed no remarkable changes or cysts. The placenta was disproportionately large (21 by 17 by 4 cm.), thick and edematous, weighing 650 Gm.

Sections from the malformed lower lobe of the left lung revealed numerous small cystic spaces lined by a single layer of cuboidal epithelium and surrounded by scanty fibrous stroma. These structures apparently represented much dilated terminal bronchioles. Scattered among them were a smaller number of much larger, irregular-shaped cystic spaces lined by pseudostratified columnar epithelium, often ciliated, and surrounded by a basement membrane with a mantle of well developed smooth muscle. These apparently represented the larger bronchioles, but no cartilage or mucous glands could be found in their walls. In places a third type of glandular structure was observed, lined by a single layer of tall columnar epithelium with clear cytoplasm and basally situated nuclei, exactly similar to the epithelium of the stomach and the colon. It was surrounded by a basement membrane but was devoid of smooth muscle. Lastly, normal lung tissue was seen at the periphery (i.e., adjacent to the pleura). Between the malformed and the normal tissue there was no clear demarcation or fibrous septum.

Sections from the upper lobe of the left lung and from the right lung showed normal tissue only.

In the liver there was dilatation of the central veins, also pronounced hemopoiesis, indicating prematurity. The chorionic villi of the placenta showed capillary engorgement and edema.

The other organs revealed no significant changes.

REVIEW OF THE LITERATURE

As stated, 10 cases of a lesion of the lung similar to ours were found by a search of the available literature (table). What Nordmann [2g] called an "accessory lung" revealed histologically the same structure as the lungs showing adenomatoid malformation.

In 4 of the reported cases the subject was a male infant, in 5 a female infant and in 1 the sex was not specified. Almost all the subjects were premature infants, many stillborn.

The lesion involved only one lobe in 6 cases; it involved two lobes in 2 cases and the entire right lung in 1 case. In the remaining case (Sternberg's [2d]), which must be considered as an exception, both lungs were diffusely involved and symmetrically enlarged. Otherwise the left lung was involved 5 and the right 4 times. The lesion was a diffuse metamorphosis of an entire lobe (or lung) with a smooth contour. The bronchus leading to the lobe ended blindly or could not be further traced when its widened ramifications were reached (Koboth [2i]). It was atretic and lacked cartilage in Meyer's [2e] case.

Microscopically, all the involved lobes revealed large and small cystic spaces, lined by columnar and cuboidal epithelial cells. The larger cysts had elastic fibers and smooth muscle in the walls. Absence of cartilage was noted by Koboth and practically all the other authors (Esch,[2h] Wermbter,[2f] Meyer, [2e] Seyffert,[2c] Störk [1] and Lahm [2b]), while Koboth further noted absence of arteries and Lahm absence of mucous glands. Koboth noted the presence of tall columnar "gastric" epithelium, even with polypoid formations.

The lesion was called by various names: "Cystic malformation and excessive overgrowth of the bronchial system" (Störk); "congenital adenoma of the small bronchioles" (Seyffert; Lahm); "adenoma pulmonis" (Meyer); "tumor-like malformation" (Meyer; Koboth); "hyperplasia of lung tissue" (Wermbter); "congenital hyperplasia of the lung with deficient development of the alveoli as a result of fetal bronchiectasis" (von Graff; Sternberg), and "adenomatoid overgrowth of the lung" (Koboth). Most authors considered the condition a malformation and not a neoplasm. Lahm thought the cysts arose not only from small bronchioles but also from the infundibula and alveoli.

No one has advanced any definite cause for the condition. Graff spoke of an intrauterine hypertrophy of one lobe (or lung) when he saw that the other lung was just a rudiment. The fact that an entire lobe was malformed indicated to Koboth that the malformation started at a time when the different lobes were

Cases of Congenital Adenomatoid Malformation of the Lung from the Literature

Case	Year	Author	Sex	Age	Position of Lesion	General Anasarca	Hydramnios
1	1897	Störk [1]	M	Newborn	Right lung, middle lobe	Present	.....
2	1905	von Graff [2a]	M	2½ days, a premature infant	Left lung, two lobes	.....	.....
3	1919	Lahm [2b]	..	8 mo. intrauterine, stillborn	Left lung, upper lobe	Present	.....
4	1920	Seyffert [2c]	F	8 mo. intrauterine, stillborn	Left lung, upper lobe	Present	.....
5	1923	Sternberg [2d]	M	7 mo. intrauterine, stillborn	Both lungs	Present	.....
6	1924	Meyer [2e]	F	8 mo. intrauterine, stillborn	Right lung	Present	.....
7	1925	Wermbter [2f]	F	Premature (34 cm.)	Right lung, two lobes	Present	.....
8	1926	Nordmann [2g]	M	9 mo. intrauterine, died after a few breaths at birth	Accessory lung on left side	Present	Present
9	1928	Esch [2h]	F	9 mo. intrauterine	Right lung, lower lobe	Present	Present
10	1936	Koboth [21]	F	7 mo. intrauterine	Left lung, lower lobe	Present	.....

already separated in the lung anlage; the absence of arteries in the bronchial walls he explained by the fact that the lung anlage is formed earlier than the intrapulmonary arterial system.

A most remarkable feature of the cases is the constancy of general anasarca (see table), regarded by many as mechanical. Direct compression of the superior and inferior venae cavae was noted by Störk and Koboth. Direct compression of the right auricle was noted by Wermbter and Meyer, while Meyer's tumor also pressed on the upper part of the right ventricle. Nordmann attributed the venous stasis to compression and kinking of the superior and inferior venae cavae as a result of excessive mediastinal and cardiac displacement. Finally Seyffert explained the circulatory embarrassment by excessive positive intrathoracic pressure (due to rapid expansile growth of the lung) which interfered with the heart in diastole.

Edema of the placenta (Esch, Nordmann and Seyffert) was attributed to systemic venous stasis or cardiac failure.

Pronounced extramedullary hemopoiesis was found in the liver by Esch, Meyer and others and was taken to be compensatory for cardiac failure after an idea sponsored by Schridde,[3] but it is more likely an expression of the prematurity of the infants.

COMMENT

In our case the pulmonary condition is a malformation because (1) it involves the entire lower lobe of the left lung, (2) it lies within the confines of the left visceral pleura, (3) a branch from the left bronchus leads into the mass, (4) the malformed portion passes directly into normal-looking lung tissue at the periphery without any demarcation or encapsulation and (5) it is an organoid growth consisting of a large number of well differentiated bronchioles lined by columnar cells and surrounded by smooth muscle and a far greater number of terminal bronchioles lined by cuboidal cells with a well formed basement membrane. The essential feature is an excessive overgrowth of the bronchioles, especially of the terminal bronchioles, which causes the marked enlargement of the lobe, while the development of the alveoli is completely suppressed except at the periphery. Thus the mass can be called a hamartoma (tumor-like overgrowth of normal tissue) of the lung except that certain elements, such as cartilage, mucous glands and alveoli, are not present.

In this case, as in most of the reported cases, general anasarca was present, and there is no question that it was of mechanical origin. The lobe was so voluminous that, besides displacing the mediastinum and exerting visible traction on the venae cavae, it must have occasioned a great increase of intrathoracic pressure. This circulatory embarrassment was probably a significant factor in the fetal death in our case and in 4 of the recorded cases. Fetal death can cause premature onset of labor.

Hydramnios, which was present in our case and in 2 recorded cases, seems more than a mere coincidence. Esch's view that it is related to the fetal hydrops is supported by the occurrence of hydramnios in cases of fetal heart disease (DeLee and Greenhill[4]). Hydramnios also induces premature labor.

The presence of both factors causing prematurity in such cases accounts for the fact that in 10 of the 11 recorded cases (including ours) the subject was a premature infant.

The adenomatoid malformation of the lung is a form of, or belongs to the category of, congenital cystic lung, and indeed Koontz[5] included

3. Schridde, H.: München. med. Wchnschr. **62**:397, 1910.

4. DeLee, J. B., and Greenhill, J. P.: The Principles and Practice of Obstetrics, ed. 8, Philadelphia, W. B. Saunders Company, 1945, pp. 39 and 582.

5. Koontz, A. R.: Bull. Johns Hopkins Hosp. **37**:340, 1925.

the case of adenomatoid malformation reported by Störk as an instance of congenital cystic lung. However, cases of adenomatoid malformation of the lung form a special group, as this condition is observed almost exclusively in premature infants, usually with general anasarca and sometimes also with hydramnios, whereas congenital cystic lung is encountered more frequently in adults than in children. Of 374 cases collected by Schenck,[6] 212 concerned adults; 162, children, and in two thirds of the cases the condition was present after the fifteenth year of age. Anatomically, in the latter disease the cysts are of variable size, may or may not communicate with the bronchi, may be isolated and few or so numerous as to cause a diffuse "honeycombing" of the lung, and may involve one or more lobes of one or both lungs. The fact that coal pigment is not present in the walls of the cysts in adults is generally taken as evidence that the cysts are congenital in contradistinction to bronchiectatic cavities. In the cyst wall, cartilage is generally present but not as constantly as elastic fibers and smooth muscle, and mucous glands are present only in a moderate number of cases. Thus, there is no fundamental anatomic difference between the two conditions. According to Wilson,[7] the bronchial tree not only continues to grow in size after birth, but continues branching until the end of the seventh year. In this period the tree is still in the formative stage, and therefore malformations can still take place. Excessive size of the cysts or secondary infection determines the onset of symptoms. The patients may die either of asphyxia, due to cystic compression of lung tissue, or of suppuration. The time of onset of the malformation is evidently the deciding factor for the difference of the clinical syndrome, the mode of death and certain anatomic variations. It is remarkable that the prenatal type is so rare (10 cases up to the present) as compared with the postnatal type, which is of relatively common incidence (381 cases up to 1937, according to Schenck). As regards the primary cause of the malformation in both types, nothing definite is known other than that in certain cases the postnatal type is familial (Neisser[8]; Sandoz[8]).

A feature of interest in our case and Koboth's case was the presence of occasional small foci of tubular structures lined by a single layer of very tall columnar epithelium of the type found in the stomach and the colon, which is quite different from the pseudostratified columnar epithelium of the ordinary bronchial system. Since the lung is of endodermal origin, the presence of such tall columnar epithelium of gastrointestinal type is not entirely unexpected. Such foci of tall

6. Schenck, S. G.: Am. J. Roentgenol. **35**:604, 1936.

7. Wilson, G. H.: Am. J. Anat. **41**:97, 1928.

8. Cited by Schenck.[6]

columnar cells probably gave rise to the so-called enterocystoma of the lung (Ewing [9]), viz., small or large cysts lined by colonic epithelium inside the lung as instances of dysontogenesis. In such cases the lung tissue surrounding the cyst or cysts is quite normal.

The observation that foci of colonic epithelium are present in adenomatoid malformation of the lung brings up for discussion another condition described under the names of "adenomatosis of the lung" (Richardson [10]), "pulmonary adenomatosis" (Sims [11]; Simons [12]) and "pulmonary mucous epithelial hyperplasia" (Bell [13]; Taft and Nickerson [14]). In this condition, tumor-like nodules or masses are found in the lung and each nodule consists of glandular structures lined by tall columnar epithelium. Adenomatosis of the lung is therefore quite different from adenomatoid malformation of the lung, since the latter is a diffuse malformation without tumor-like nodules and tall columnar epithelial cells are found only in occasional small foci and do not show massive overgrowth. In passing it may be stated that conditions resembling adenomatosis but revealing the character of a true cancer in giving rise to metastases in bronchial and prevertebral lymph nodes (Briese [15]) and in bones and regional lymph nodes (Oberndorfer [16]) have been described. Furthermore, lesions resembling adenomatosis of the lung may be produced in certain infections in animals, viz., jagziekte of sheep in South Africa and Iceland and progressive pneumonia of sheep and horses in Montana (Dungal [17]; Bonne [18]; Wood [19]; Norris [20]), and, strange enough, even in this type of hyperplasia of tissues, on an infectious basis, Aynaud [21] has found metastasis to the hilar lymph nodes. In this infectious type and in human adenomatosis of the lung, the tall columnar epithelial cells arise, it is believed, from the bronchiolar and alveolar epithelium by metaplasia as a reaction to chronic irritation, rather than from embryonic cell rests.

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9. Ewing, J.: Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 1065.
10. Richardson, G. O.: J. Path. & Bact. **51**:297, 1940.
11. Sims, J. L.: Arch. Int. Med. **71**:403, 1943.
12. Simons, M. A.: Am. J. Path. **23**:413, 1947.
13. Bell, E. T.: Am. J. Path. **19**:901, 1943.
14. Taft, E. B., and Nickerson, D. A.: Am. J. Path. **20**:395, 1944.
15. Briese, cited by Bonne.[18]
16. Oberndorfer, S.: Virchows Arch. f. path. Anat. **275**:728, 1930.
17. Dungal, N.: Proc. Roy. Soc. Med. **31**:497, 1938.
18. Bonne, C.: Am. J. Cancer **35**:491, 1939.
19. Wood, D. A., and Pierson, P. H.: Am. Rev. Tuberc. **51**:205, 1945.
20. Norris, R. F.: Arch. Path. **43**:553, 1947.
21. Aynaud, cited by Sims [11] and by Dungal.[17]

SUMMARY

A case of congenital adenomatoid malformation of one lobe of a lung is reported. Only 10 similar cases have been described in the literature. The mechanical circulatory embarrassment may cause death of the fetus. Hydramnios was present in 3 of the 11 cases and is possibly related also to the fetal hydrops.

The condition is of the nature of a malformation which starts when the lung anlage has already undergone lobulation but cartilage, arteries, mucous glands and alveoli are not yet differentiated. The lesion is more than a simple malformation, however, since there is an overgrowth of the bronchioles—a hamartoma, which is responsible for the enlargement.

Congenital adenomatoid malformation of the lung belongs to the general category of congenital cystic lung, but forms a special subgroup by itself.

BEHAVIOR OF HODGKIN'S DISEASE NODES TRANSPLANTED INTO THE ANTERIOR CHAMBER OF THE RAT'S EYE

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AND
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THIS study was undertaken in order to observe the behavior of Hodgkin's disease tissue and the reaction induced by it after it had been transplanted to the anterior chamber of the rat's eye.

The method of study adopted was that of Greene,[1] who has utilized the anterior chamber of the eye for transfers of homologous and heterologous embryonic and neoplastic tissue.

Although it was known to us (by personal communication) that Greene had failed to obtain any "takes" in some 20 Hodgkin's tissue transplants, repetition of this work was considered justified for a number of reasons:

1. We wished to determine whether failure of transplantation could be correlated with the various types of histologic pattern encountered in this disease.

2. We wished to study the early changes in the transplant and the iris reaction of the host, comparing these with control material. The iris reaction was to be followed to see whether a specific inflammatory reaction occurred, and thus secure a clue to the presence of a possible etiologic agent.

3. Since tissue culture studies of Hodgkin's disease nodes were already in progress, it seemed advisable to extend the experiment to include parallel transplantation of both fresh tissue and fragments which had been maintained in tissue culture. We hoped to determine whether a period of in vitro cultivation would alter the biologic properties of the tissue as far as transplantability is concerned.

MATERIALS AND METHODS

White rats ranging from 2 to 4 months of age were used as hosts for the majority of the transplants. Rats were chosen mainly because an active colony was

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1. Greene, H. S. N.: J. Exper. Med. **73**: 461, 1941.

available and also because it seemed pointless to use guinea pigs, since they had already been shown to be of no value for Hodgkin's disease transplants. Mice proved to be unsuitable because of technical difficulty in effecting the transfer of the tissue without producing traumatic cataracts. A few rabbits were used, but since the results were negative, we concentrated on the rats.

The number of rats used for each experiment varied from 3 to 19. Most of them were killed at intervals of five to ten days for microscopic examination of the transplant and the eye tissues; a few were retained for longer periods, up to six months.

The transplantation technic was that of Greene, who gave us personal instruction in this technic.

The tissues used were, with one exception, of human origin. For the main portion of the experiment we used lymph nodes removed at operation from 27 patients. Portions of full term placenta were also transferred as an example of presumably inert tissue for comparison. Rat embryo tissues were used as a control of the technic and, finally, we injected tissue culture medium alone as a control for the cultured fragments.

Thirteen of the lymph nodes showed Hodgkin's disease. The remainder of the nodes manifested various lesions, including lymphoid hyperplasia (2 nodes), tuberculous lymphadenitis (1), reticulum cell sarcoma (3), lymphosarcoma (2) and metastatic carcinoma (6).

Of the 13 Hodgkin's disease transplants, 7 were fresh tissue and 11 were tissue culture fragments; double transfers of both fresh and cultured tissue were carried out in 5 instances. The various lymphoid controls were evenly divided between fresh and cultured fragments.

The Hodgkin's disease lymph nodes presented varying histologic patterns. According to the classification of Jackson and Parker,[2] 2 of these were paragranuloma, 10 were granuloma and 1 was Hodgkin's sarcoma. Four of the nodes were markedly fibrotic.

The cultures were grown by Miss Augusta Hollender, in Carrel flasks, type D-5, in a medium consisting of a mixture of chick plasma, chick embryo extract, Tyrode's solution and human umbilical cord serum in the solid phase, and chick extract, human cord serum and Tyrode's solution in the fluid phase. From 20 to 25 fragments, each about 1 cu. mm., were placed in each flask. Since it was impossible to dissociate the tissue culture fragments from the tenacious medium, the latter was also introduced into the animal's eye along with the tissue. Control studies subsequently proved that the medium was bland.

The cultures were in most instances forty-eight to seventy-two hours old at the time of transplantation, the time being selected according to the richness of the outgrowth and the number and the type of cells in the zone of migration, both of these phenomena being quite variable. In 2 cases we used six week cultures composed entirely of sheets of fibroblasts. One of these was from a node showing Hodgkin's disease; the other, from one showing lymphoid hyperplasia. The control tissue culture material, other than the six week culture of a hyperplastic node consisted of cultures of tissues presenting metastatic carcinoma of the thyroid gland, tuberculous lymphadenitis, lymphoid hyperplasia, reticulum cell

2. Jackson, H., Jr., and Parker, F., Jr.: Hodgkin's Disease and Allied Disorders, New York, Oxford University Press, 1947.

sarcoma (2 cases) and lymphosarcoma. All these had been maintained for forty-eight to seventy-two hours in Carrel flasks before portions were transplanted to the eye.

Fate of Transplanted Fragments.—Regardless of the inherent lesion of the transplanted lymphoid tissue, in the eye the behavior of the transplant followed a set pattern.

During the first week the fragment was grossly observed to be surrounded by a filmy halo. Microscopic sections showed this to be a clear coagulum. In some instances the fragment slowly disintegrated and eventually disappeared in the first ten to twenty days. In others it became dense and white, with irregular edges, retaining in general the shape of the original fragment but decreasing slightly in size. If the fragment was still visible after two to three weeks, it usually remained unchanged until the animal was killed, even up to six months after transplantation.

Microscopic examination at five to ten day intervals showed that, with the exception of a few lymphocytes, the loose cellular constituents of the transplant disappeared during the first week, leaving only a small fibrous mass, the center of which in many instances showed degeneration and necrosis. Those fragments which grossly appeared dense and white after thirty or more days in the anterior chambers were composed of acellular, avascular fibrous tissue.

Sternberg-Reed cells were not observed in any of the Hodgkin's disease fragments even when they were examined by serial section as early as three days after transplantation.

All control tissues, both fresh and cultured, showed essentially the same changes as those described for Hodgkin's disease tissue. No "takes" were obtained. Those fragments which did not undergo early necrosis and autolysis eventually became fibrotic.

Iris Reaction.—In all instances the transplanted fragment adhered to the iris at one point or another, and there was usually a marked lymphocytic reaction in the iris along the line of attachment. Rarely eosinophilic leukocytes infiltrated the site of attachment, usually to a slight degree. After the first week, giant cells with numerous peripheral nuclei were frequently observed both in the iris at the point of attachment and in the periphery of the transplant itself, surrounding the central necrotic zone.

The lymphocytic reaction of the iris was most intense in those animals which were killed during the first week and in which the transplant showed extensive necrosis. Fibrotic fragments were usually accompanied by only a slight reaction of the iris.

No Sternberg-Reed cells were ever observed in serial sections through the eye.

Essentially the same iris reaction was seen with the fresh tissue and with the cultured controls, regardless of the inherent pathologic process in the tissue before transplantation. The same changes were noted around a fragment of normal human placenta as around fragments of reticulum cell sarcoma and tissues showing varying histologic types of Hodgkin's disease.

The tissue culture medium alone produced no iris reaction.

COMMENT

Like the guinea pig used by Greene, the rat proved to be a poor host for lymphoma planted in the anterior chamber of the eye.

Our lack of success with the transplantation of cancer tissues used for control purposes may be largely due, again, to the fact that the rat is a poor host for heterologous transplants. Homologous transplants of rat embryo grew well, almost filling the chamber in two weeks. This demonstrated to us that the failures with heterologous tisue were not due to error in the technic of transfer.

Tissue grown first in vitro and later planted in the anterior chamber fared no better than fresh tissue.

The reaction of the host rat to all heterologous tissue planted in the eye was of a chronic inflammatory nature and nonspecific in type. We failed to find anything which could be interpreted as conforming to a Hodgkin's disease pattern.

HYPERTENSIVE CARDIOVASCULAR DISEASE

An Experimental Study of Tissue Changes in Bilaterally Nephrectomized Dogs

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THAT the kidney plays an important role in the genesis of hypertensive cardiovascular disease ("malignant hypertension") is generally accepted, but the mechanism involved is still a matter of controversy. Thus many [1] believe that this disease results from the action of a pressor substance produced by the ischemic or otherwise disordered kidney; others [2] maintain that some renal incretory function is in abeyance. Others look on the disease as an ill defined reaction to stress related to such diverse clinical states as rheumatic fever or periarteritis nodosa.[3] Bilateral nephrectomy affords an obvious procedure for elucidating the role of the kidney in the genesis of hypertensive cardiovascular disease and has been performed by numerous investigators. Since this operation has not resulted consistently in the development of the two major characteristics of the disease (an elevated blood pressure and arteriolar lesions), previous workers have concluded that the presence of altered renal tissue is necessary for the development of this disorder.[4] However, in none

This work was supported by a grant from the Life Insurance Medical Research Fund.

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1. Goldblatt, H., in Harvey Lectures, Baltimore, Williams & Wilkins Company, 1938, p. 237.

2. Grollman, A., in Pincus, G.: Recent Progress in Hormone Research, New York, Academic Press, Inc., 1947, vol. 1, p. 371.

3. Selye, H.: Ann. Int. Med. **29**:403, 1948.

4. (*a*) Goldblatt, H.: Ann. Int. Med. **11**:69, 1937. (*b*) Winternitz, M. C.; Mylon, E.; Waters, L. L., and Katzenstein, R.: Yale J. Biol. & Med. **12**:623, 1940. (*c*) Cash, J. R.: Proc. Soc. Exper. Biol. & Med. **23**:609, 1926. (*d*) Hartwich, A.: Ztschr. f. d. ges. exper. Med. **69**:462, 1930. (*e*) Harrison, T. R.; Mason, M. F.; Resnik, H., and Rainey, J.: Tr. A. Am. Physicians **51**:280, 1936. (*f*) Katz, L. N., and others: Am. Heart J. **17**:334, 1939. (*g*) Braun-Menendez, E., and others: Hipertension arterial nefrogene, Buenos Aires, El Ateneo, 1943.

of their studies was it possible to prevent the relatively early effects of the uremic state, and one could, therefore, always attribute the observed negative results to the poor state of the animals and their short period of survival following nephrectomy. As a matter of fact, in some of these earlier experiments occasional animals that did not deteriorate too rapidly displayed moderate to prominent elevations of blood pressure.[5] These isolated examples of hypertensive vascular disease following bilateral nephrectomy, being exceptional rather than the rule, were disregarded in the ultimate conclusions drawn from these experiments.

In the present study we have reinvestigated the effects of nephrectomy on the blood pressure and the pathologic changes induced by this operation. By prolonging the life of our animals and concomitantly improving their general state of health, it has been possible to obtain consistent results and to obviate the objections raised against previous work in this field. The prolongation of the life of the nephrectomized dog was made possible by the use of electrolyte-free diets and the application of an artificial kidney, the use of which has been reported elsewhere.[6] By these procedures, it has been demonstrated that in the dog bilateral nephrectomy is followed consistently by an elevation of blood pressure, which frequently reaches high levels.[7] In the present communication we wish to present results dealing with the other accepted component of hypertensive cardiovascular disease, viz., the morphologic changes occurring throughout the body.

The most informative of the extant studies on the effects of bilateral nephrectomy in dogs is that of Winternitz, Mylon, Waters and Katzenstein,[8] 1 of whose animals survived ten days, while 6 survived on the average slightly over seven days. Although in these 6 dogs there was a tendency for the blood pressure to rise, in 1 instance reaching levels as high as 200 mm. of mercury (mean pressure), these authors disregarded these rises and concluded "that the kidney is not primarily concerned in the maintenance of the normal blood pressure." The blood nonprotein nitrogen of their animals, the acidosis and the hypochloremia reached significant proportions, but at autopsy these workers encountered no specific gross lesions. Occasional subendocardial, valvular and visceral hemorrhages and focal necrosis involving heart muscle and the smooth muscle of the arterial wall

5. Winternitz and others.[4b] Harrison and others.[4c]

6. Vanatta, J.; Muirhead, E. E., and Grollman, A.: Am. J. Physiol. **156**:443, 1949.

7. Grollman, A.; Muirhead, E. E., and Vanatta, J.: Am. J. Physiol. **157**:21, 1949.

8. Winternitz, M. C.; Mylon, E., and Katzenstein, R.: Yale J. Biol. & Med. **13**:595, 1941; footnote.[4b]

and of the alimentary and genitourinary tracts were observed after careful search but only in minimal degrees. Ligation of both renal arteries or of both ureters, on the other hand, was found to be associated with great accentuation of these lesions. If crude kidney extracts were injected after bilateral nephrectomy, there was accentuation of these lesions and of the elevation of blood pressure. Winternitz and associates concluded, therefore, that renal extracts contained pressor, necrotizing and hemorrhagic factors which presumably were the responsible agents in the causation of "malignant hypertension" as suggested by Goldblatt.[1] Winternitz and associates, however, described various morphologic changes in the body with greater thoroughness and attempted to separate pressor and lesion-inducing factors present in renal extracts. These authors realized that material absorbed from necrotic kidneys could not be the only factor responsible for the observed lesions, since similar, although minimal, changes occurred following bilateral nephrectomy alone.

The observations and interpretations of Winternitz and associates are emphasized here because our observations of the morphologic changes induced in dogs by bilateral nephrectomy are consistent with their earlier work, although the interpretations given these findings differ widely. The widespread fulminant lesions described by Winternitz and co-workers as following ligation of the ureters and the injection of renal extracts in nephrectomized animals have been observed by us following bilateral nephrectomy alone. Moreover, as mentioned in a foregoing paragraph, such animals under our experimental conditions consistently displayed after nephrectomy a rising blood pressure which attained significant proportions by the seventh to tenth day. Thus, under the proper conditions a hypertensive vascular disease does follow bilateral nephrectomy and is accompanied by the lesions characteristic of "malignant hypertension."

The present observations are based on the gross and microscopic changes occurring in two groups of 71 dogs after bilateral nephrectomy. The first group, consisting of 27 animals, received electrolyte-free food but were allowed to die in uremia without being attached to the artificial kidney. In the second group, of 44 dogs, survival and improved body state were extended by the use of an electrolyte-free diet plus periodic application of the artificial kidney. The former group serves as a control so far as any effects that might be induced by the artificial kidney are concerned.

In addition to observing dogs, we have examined the tissues of patients coming to autopsy to correlate the experimental findings with those observed in the human subjects. To demonstrate the identity of the experimental and clinical findings, we have included the study of the human tissues in the present report.

METHODS

Adult mongrel dogs were used throughout. The technics used in performing the nephrectomies and in the application of the artificial kidney are described elsewhere.[9] By a modification of the precedure of Kolff and Noordwijk,[10] in vivo dialysis was conducted for three hours at intervals of 3 to 5 days. At the end of the dialysis, if there was severe anemia, transfusions of concentrated red blood cells (properly cross matched) were given. Electrolyte-free food and water were offered the animals ad libitum.

Promptly after the death of the animals, autopsies were made, and the tissues were fixed in 4 per cent formaldehyde solution. These were prepared in the usual manner and stained with hematoxylin and eosin. On a few occasions Masson's trichrome stain as modified by Goldner [11] was also utilized. The tissues were selected from areas showing pathologic changes grossly or, when no such changes were evident, were taken by multiple random sampling.

Several different types of controls were available. Any effects induced by the artificial kidney were controlled as mentioned in a foregoing paraprah. The ablated kidneys acted as specific controls for each animal. In addition, tissues were taken from the following group of normal dogs after the stated manipulations and compared with the tissues from the nephrectomized animals: (1) animals used as blood donors; (2) animals subjected to in vivo dialysis with the artificial kidney; (3) animals whose tissues were allowed to autolyze prior to fixation; (4) animals receiving large doses of heparin, and (5) animals subjected to various types of oligemic shock.[12]

Mean blood pressures were obtained by direct puncture of the femoral artery and a mercury manometer.[13]

RESULTS

Blood Pressure.—Although the specific blood pressure effects of bilateral nephrectomy and other renal manipulations are discussed in detail elsewhere,[7] the scatter graph of figure 1 is given here to indicate the tendency of blood pressures to rise after nephrectomy in animals not aided with the artificial kidney (average survival, 4.7 days), as well as in those in which survival was prolonged (average survival, 7.1 days) by the use of the artificial kidney.

Survival.—The survival period of all the animals varied between 3 and 19.5 days. The 19.5 day survival constitutes the longest survival of a bilaterally nephrectomized dog with which we are familiar.

The survival period may be analyzed by separating the dogs into three groups, which are listed in frequency distribution style in table 1. The first group consists of 27 animals that died without being attached to the artificial kidney. In this group the average survival in the 20 instances in which the exact period of survival was known amounted to 4.7 days (113 hours). Sixty-five per cent of this group survived between 5 and 6+ days. The second group consists of 31 animals

9. Vanatta and others.[6] Grollman and others.[7]

10. Kolff, W. J., and Noordwijk, J.: The Artificial Kidney, Kampen, Holland, J. H. Kok, 1946.

11. Goldner, J.: Am. J. Path. **14**:237, 1938.

12. (*a*) Muirhead, E. E.; Kregel, L. A., and Hill, J. M.: Arch. Surg. **47**:258, 1943. (*b*) Muirhead, E. E., and Hill, J. M.: J. Lab. & Clin. Med. **29**:239, 1944.

13. Grollman, A.: Am. J. Physiol. **147**:647, 1946.

succumbing after one application of the artificial kidney. In this group the average survival extended to 6.2 days (149 hours), and 70 per cent of this group survived for 6 to 8 days or longer. The third group, of 11 animals, were aided with the artificial kidney on 2 occasions and survived between 8 and 9+ days (average, 9.0 days or 216 hours).

Although the use of an "artificial kidney" and an "electrolyte-free" diet extends the survival of bilaterally nephrectomized animals, in view of the lesions to be described next it is not surprising that survival is not prolonged indefinitely. The generalized degenerative effects, particularly those involving the heart and the blood vessels, apparently do not allow for an indefinite survival.

Gross Lesions.—The gross changes that were present in each instance consisted of generalized hyperemia of the viscera, pulmonary edema and cardiac

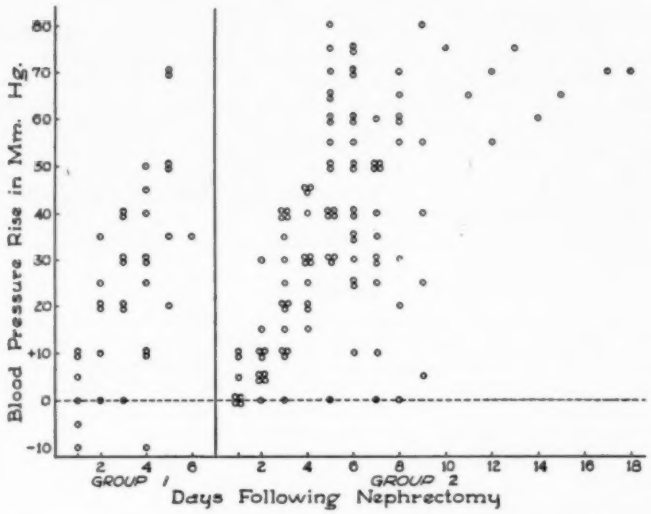

Fig. 1.—A scatter graph of the blood pressures observed following bilateral nephrectomy in dogs. At the left are readings on dogs not subjected to dialysis (group 1), at the right, data on animals treated by dialysis with the artificial kidney (group 2).

dilatation, more prominent on the right side. The next most commonly encountered change consisted of hemorrhages. In the heart these were found most consistently in the subendocardial tissue of both the right and the left ventricle but preponderantly in the latter. They usually involved the papillary muscles, the apex and the intraventricular septum from its midportion down toward the apex. At times, intramural myocardial hemorrhages were evident grossly. Pulmonary hemorrhages were likewise common. These involved the parenchyma but were evident from the pleural surfaces. The hemorrhagic areas were usually round and measured 2 to 5 mm. in diameter. They were scattered throughout all lobes but were more frequent in the lower lobes. Occasionally, large pulmonary hemorrhages were encountered; less commonly, confluent hemorrhages gave rise to focal or

lobar hemorrhagic consolidation. Pulmonary infarcts were rarely encountered. Next in frequency were hemorrhages of the gastrointestinal tract, which usually involved the entire tract from stomach to rectum. In the stomach the hemorrhages were found mostly in the mucosa and submucosa and at times extended into the lumen. Rarely an animal seemed to succumb to a massive gastric hemorrhage. The hemorrhages of the intestine were usually in the muscularis and serosa. Again in rare instances massive intestinal hemorrhage occurred. Intussusception of the intestine was observed to occur in 11 per cent of the entire group, with over 60 per cent of the intussusceptions occurring after the seventh day. These were associated with hemorrhagic infarction, obstruction and hemorrhages into the bowel.

Microscopic Lesions.—Microscopically, certain consistent alterations, such as changes associated with circulatory disturbances and usually ascribed to congestive heart failure, were observed in the entire group. Generalized visceral venocapillary hyperemia was prominent and affected heart, lungs, abdominal viscera and brain. In addition, the heart at times displayed interstitial edema.

TABLE 1.—*The Survival of Bilaterally Nephrectomized Dogs With and Without the Application of the Artificial Kidney*

Group 1 Not Subjected to Artificial Kidney		Group 2 Subjected to Artificial Kidney Once		Group 4 Subjected to Artificial Kidney Twice	
Dogs	Period of Survival, Days	Dogs	Period of Survival, Days	Dogs	Period of Survival, Days
2	3 to 3+	3	4 to 4+	4	8 to 8+
5	4 to 4+	6	5 to 5+	7	9 to 9+
10	5 to 5+	9	6 to 6+		
3	6 to 6+	11	7 to 7+		
		2	8 to 8+		
Average	4.7		6.2		9.0

The lungs were consistently the seat of hyperemia, edema and focal capillary hemorrhages. Eosinophilic emboli were observed within the small vessels of the lungs, associated with certain of the pulmonary hemorrhages, in 16 dogs, 2 of which were in group 1 (no in vivo dialysis). In structure these embolic masses were lumpy and granular and resembled the smudged media of the arteries to be described. At times they contained entrapped nuclear remnants, suggesting a causal relationship to the smudged vessels, and 12 of these animals, 10 of which survived 7 days or longer, had prominent smudging of arterial media elsewhere in the body. The pulmonary edema on each occasion involved the dependent areas and at times was severe and generalized. In the latter instances, the bronchi and the trachea were filled with a frothy pink fluid. Focal atelectasis occurred, usually in the presence of more prominent hemorrhages.[14] The hyperemia of the liver was associated with centrolobular damage, usually in the form of central atrophy but in more severe cases in the form of central fatty metamorphosis or outright central necrosis. Not infrequently, the adrenal cortex was found to be prominently infiltrated with polymorphonuclear neutrophilic leukocytes. (This finding has been observed frequently following fatal oligemic shock due to a severe

14. A small percentage of the dogs had chronic interstitial pneumonitis. This change apparently constituted a previously existent state and did not seem to alter the findings except in the lungs.

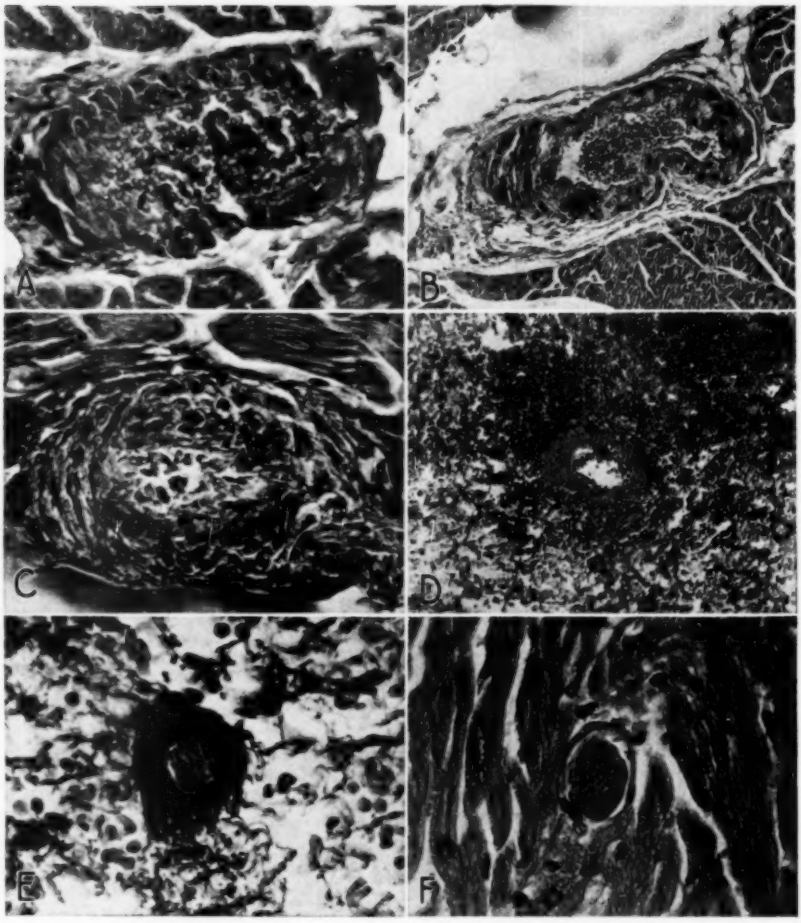

Fig. 2.—The vascular lesions, in various stages of development, as observed in nephrectomized dogs with hypertensive cardiovascular disease: *A* (dog 28; survival, 5 days; blood pressure, 150; no dialysis), small artery of the myocardium showing degeneration and necrosis of the smooth muscle fibers of the media. Notice the hyaline swelling of fibers, absence of nuclei focally with early lumpy granular change of the sarcoplasm, and the hyaline swelling of other fibers with pyknotic nuclei. The individual cell boundaries are maintained by most fibers, although early smudging can be seen in the left lower area. × 211.5.

B (dog 75; survival, 7¼ days; blood pressure, 135; subjected to one dialysis), small artery of the myocardium showing degeneration and necrosis of the media more advanced than in *A*. Most fibers have lost their nuclei and

(Legend continued on next page)

freeze [12a] and following fatal burns.[15] The observation, therefore, does not seem to have a specific connotation). The brain usually displayed microscopic "collar" hemorrhages into the Virchow-Robin spaces.

Aside from the circulatory disturbances that can be considered as due mainly to congestive heart failure, there were specific microscopic changes at various sites. Certain of these morphologic changes are considered by workers in this field as a necessary component of so-called malignant hypertension; namely, the arterial and arteriolar necrosis or the "necrotizing arteriolitis" of Fahr.[16] In its ultimate state this lesion consisted of necrosis of the media with an eosinophilic smudging of the vessel wall and had all of the features usually ascribed to it, including in addition to the smudging (1) focal or segmental involvement of a given vessel, (2) partial or complete circumferential involvement, (3) intact endothelium without thrombosis, (4) rupture of an occasional vessel with hemorrhage, (5) spreading of the eosinophilic substance into the adventitial and periadventitial areas, (6) narrowing of the lumen of smaller vessels and (7), in isolated instances, spreading of the eosinophilic substance into the lumen. On very rare occasions the adventitia of a smudged artery contained a few scattered round cells of the lymphocytic series. Polymorphonuclear leukocytes, eosinophilic granulocytes, fibrinoid degeneration and other features of periarteritis nodosa were not observed. Moreover, in these same animals other arteries failed to display this peculiarity. Klemperer and Otani [17] noted the same finding in malignant hypertensive vascular disease of human beings.

It is believed that the mechanism of this arterial and arteriolar necrosis can be defined better on the basis of the findings in other vessels with or without slight smudging. There appeared to be alterations of the vessel wall which might be considered as precursors of the ultimate smudging effect and which constituted a part of the generalized smooth muscle effect to be discussed subsequently. The smooth muscle fibers of the media not infrequently revealed a swelling of the

15. Dunphy, J. E., and Gibson, J. G.: Surg., Gynec. & Obst. **72**:832, 1941.

16. Fahr, T.: Virchows Arch. f. path. Anat. **226**:119, 1919.

17. Klemper, P., and Otani, S.: Arch. Path. **11**:60, 1931.

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display hyaline swelling with retention of cell outlines. The endothelium is intact, and the luminal blood is not clotted. × 166.5.

C (dog 26; survival, 4 days; blood pressure, 160; no dialysis), small artery of skeletal muscle. The inner half of the media around the circumference displays necrosis of the smooth muscle fibers. The outer half shows hyaline swelling of sarcoplasm and pyknosis of nuclei. There appears to be a tendency for the inner necrotic portion to slough into the lumen. × 211.5.

D (dog 40; survival, 9¼ days; blood pressure 200; 2 dialyses), small artery of the submucosa of the stomach showing complete necrotic smudging of the media. The endothelium is intact and the luminal blood is not clotted. The eosinophilic smudge has spread into the adventitia. Scattered cells of the lymphocytic series are seen in the adventitia. The adjoining connective tissue is edematous and has been the seat of a recent hemorrhage. × 166.5.

E (dog 40; survival, 9¼ days; blood pressure, 200; 2 dialyses), arteriole of the submucosa of the stomach showing necrosis of media with hyaline smudging. The lumen contains some of the smudged material, and the surrounding connective tissue is edematous and hemorrhagic. × 294.

F (dog 14; survival, 8¼ days; blood pressure, 160; 2 dialyses), capillary of a viable area of the myocardium, occluded and distended by eosinophilic smudged material. The endothelial wall is intact. Such structures suggest sloughing of necrotic media into the lumen of an artery or an arteriole, with plugging of adjacent capillaries. × 750.

sarcoplasm, with the usual fine and delicate longitudinally striated appearance (the change ascribed to myofibrils) giving way to a diffuse, dense and hyaline appearance. The fibers still retained their close apposition and remained as individual units, but the sarcoplasm was obviously altered. Associated with this cytoplasmic change was a prominent degree of pyknosis of the nuclei. From this change there appeared to be a transition into karyorrhexis or karyolysis of the nuclei and a fusion of the hyaline material into the eosinophilic smudge. Obviously, where the smudging had already occurred, one could not be certain that these seemingly preliminary changes had preceded it, but concomitant existence of the two changes was so common as to constitute strong collateral evidence for this view.

The arterial and arteriolar lesions involved mainly the "intimate vasculature" of the viscera. The two most common sites were the heart and the gastrointestinal tract. Much less frequently the lesion was encountered in the periadrenal connective tissue, the liver, the esophagus and the omentum. Only twice was the ultimate smudging change seen in random sections of skeletal muscle, and only once was it observed to involve the meningeal vessels.

Usually partially or completely smudged vessels retained their endothelial lining. On a few occasions, however, there appeared to be spilling of the eosinophilic substance into the lumen with partial or complete blockage. In certain cases it was possible to observe a capillary with intact wall and a plug of this substance within the lumen, forming a cast. No instance of classic thrombosis (thrombocytic column, fibrin, red and white blood cells) was observed in the entire series.

Eleven dogs displayed focal necrosis of the gastric mucosa and submucosa. This was usually associated with necrosis of submucosal arterioles, hemorrhages and collections of polymorphonuclear neutrophilic leukocytes. Focal necrosis of similar type was less commonly observed in the intestinal mucosa, the adrenal glands, the pancreas and the liver. In some cases hemorrhages were observed in the superficial zones of the gastric mucosa without the demonstration of arteriolar necrosis. Here there appeared to be disintegration of superficial capillaries.

The other main specific alteration involved the muscle tissue elsewhere in the body, particularly the myocardium. The changes were observed to involve isolated segments of individual muscle fibers, small groups of fibers and at times relatively large areas, as the greater portion of a papillary muscle. The earlier phases of this change were evident where an isolated segment of an otherwise intact fiber was affected. Here the sarcoplasm lost its cross striations and became transformed into a lumpy granular eosinophilic mass. These lumpy areas frequently became arranged transversely and alternated with clearer zones which had a moth-eaten appearance. Where nuclei remained in these areas, they were pyknotic and shriveled, but the wall of the fiber remained intact. When several adjoining fibers were involved, at times the walls were intact and at other times there was fusion of the eosinophilic substance. Under such circumstances hemorrhages also occurred. The larger areas of involvement showed similar changes but to a more advanced degree. Some fibers retained their sarcolemma while others coalesced. Hemorrhages were prominent and, in addition, polymorphonuclear neutrophilic leukocytes infiltrated the area to a prominent degree. At no time was suppuration observed. In some instances smudged blood vessels were prominent in these zones but in others a close search and additional sections through the area failed to reveal their presence. Another modification of the same process was seen in areas where no fiber remnants could be identified and only microscopic pools of

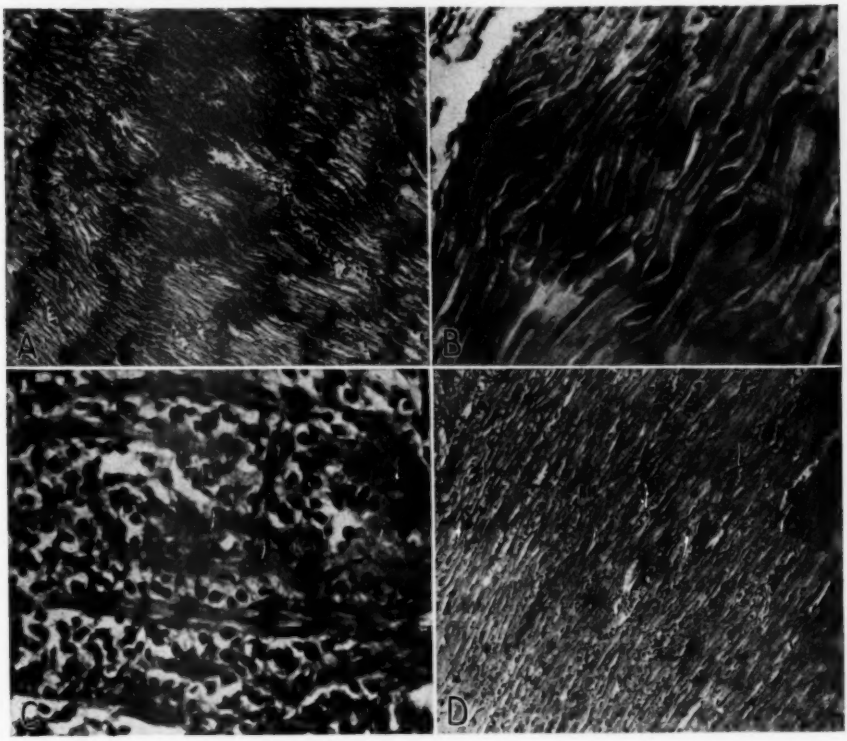

Fig. 3.—Lesions of smooth muscle as observed in dogs in which hypertensive cardiovascular disease developed following bilateral nephrectomy: *A* (dog 21; survival, 5 days; blood pressure, 140; no dialysis), circular layer of the muscular coat of the small intestine showing irregular transverse bands (palisades) of degenerated smooth muscle fibers. The fibers display individual hyaline swelling of the sarcoplasm and pyknosis of the nuclei. Between these zones the fibers are of near normal thickness. Such bands have suggested foci of contraction and degeneration. × 50.

B (dog 24; survival, 6¼ days; blood pressure, 170; no dialysis), circular layer of the muscular coat of the small intestine showing a focus of smooth muscle degeneration and necrosis. The fibers are markedly swollen and hyaline. In some the nuclei are pyknotic; in others they are absent. × 199.

C (dog 42; survival, 4 days; blood pressure, 140; no dialysis), mucosal villus of the small intestine showing hyaline swelling and pyknosis of smooth muscle fibers. The sarcoplasm has undergone hyaline change in focal areas, giving the fibers a bulbous appearance. × 199.

D (dog 79; survival, 9¼ days; blood pressure, 190; 2 dialyses), necrosis of smooth muscle of the circular coat of the large intestine. Hyaline swelling and lumpy granular changes are seen. Neutrophils have infiltrated this area. × 60.5.

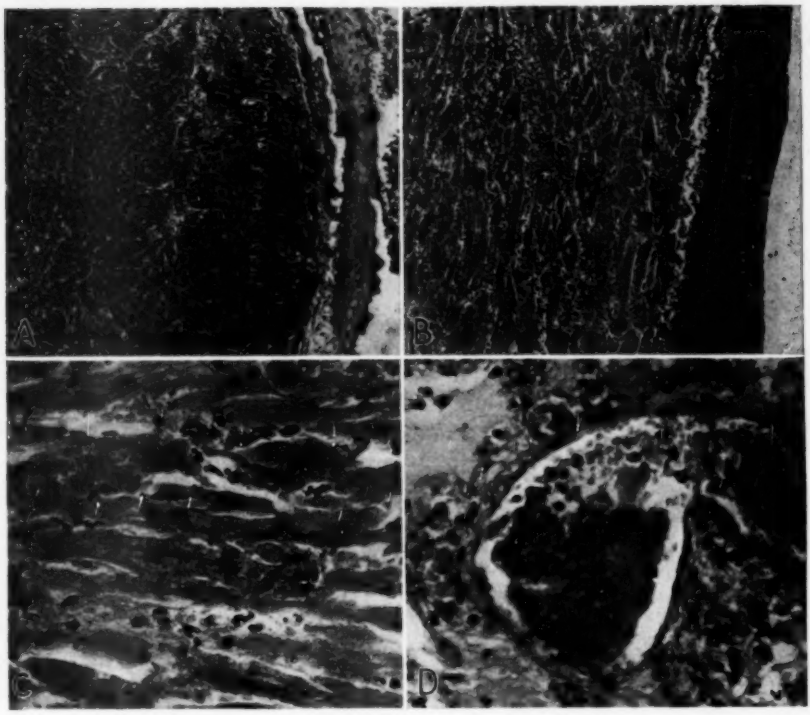

Fig. 4.—Cardiac and pulmonary lesions occurring in dogs in which hypertensive cardiovascular disease developed following bilateral nephrectomy: *A* (dog 17; survival, 7½ days; blood pressure, 150; 1 dialysis), necrosis of the myocardium near the endocardium. A blood vessel near the center of the necrotic area shows degeneration and necrosis of the media. × 42.

B (dog 14; survival, 8¼ days; blood pressure, 160; 2 dialyses), subendocardial hemorrhage and subjacent necrosis of the myocardium. The area of necrosis shows hemorrhage and collection of neutrophils. × 59.5.

C (dog 14; survival, 8¼ days; blood pressure, 160; 2 dialyses), higher magnification of necrotic myocardium. Notice transverse hyaline bands and an intervening granular, moth-eaten appearance. The cell boundaries are intact in most fibers, although early coalescence can be seen. At the top, a small blood vessel is plugged with necrotic material. × 196.5.

D (dog 78; survival, 6 days; blood pressure, 160; 1 dialysis), eosinophilic, lumpy, granular embolus in a pulmonary vessel. Nuclear remnants are seen within the embolus. There is no clotting about this structure. Such emboli have suggested an origin from sloughed media of systemic necrotic blood vessels. They have always been seen in smaller branches of the pulmonary vessels. × 196.5.

blood were visible. Usually these pools were surrounded by degenerated fibers. On four occasions the para-adventitial area of smudged vessels of the myocardium displayed prominent numbers of "myocytes."

The foci of myocardial degeneration and necrosis were most commonly encountered near the endocardium and adjacent to the areas of subendocardial hemorrhages. However, they were also observed within the wall of the ventricle several millimeters from the endocardium.

It is evident that the changes described in the foregoing paragraph differ markedly from the accepted picture of myocardial infarction as ordinarily encountered in coronary atherosclerosis. There is no coagulation necrosis, disintegration of fibers constituting the main change. Moreover, the changes observed in isolated fibers support the concept of primary myocardial degeneration and subsequent necrosis.

Smooth muscle tissue other than that of vessel walls also displayed prominent changes. These changes simulated the changes of the vessels occurring before smudging, but with additional variations. The most common site of involvement was the intestinal tract, where the circular and longitudinal layers and the fibers of the villi were affected. In the circular and longitudinal layers the process either was diffuse, involving the entire circumference or sectors, or was in the form of transverse bands involving single fibers or groups of fibers.

The individual fiber changes also consisted of swelling of the sarcoplasm with a hyaline eosinophilic transformation and pyknosis. At times, the entire fiber became prominent, while at other times there were focal bulbous swellings. On occasions, the nuclei disappeared focally. Smudging was a very rare finding, but on occasions polymorphonuclear leukocytes infiltrated the necrotic areas. In some instances there seemed to be dissolution of the muscle fibers and replacement by pools of blood. In the area of intussusception these changes plus classic hemorrhagic infarction were noted.

The intestinal changes described comprise the most commonly observed lesions. As a rule, they were more pronounced in the large bowel, where in some instances the bands of hyalinized fibers resembled foci of severe contraction. In other instances, the foci of hyalinization appeared as oval swellings between which the normal-appearing muscle was narrow, giving the entire layer a sausage-like configuration. Smooth muscle changes of a similar but less intense type were observed less commonly in the stomach, the urinary bladder, the lower part of the esophagus and the aorta.

Degeneration of skeletal muscle was encountered sufficiently often to warrant mention. However, the frequency did not approximate that of the lesions in the intestines and the heart. They were observed in random sections of skeletal muscle, esophagus and diaphragm. On occasions scattered, isolated fibers at these sites showed a loss of cross striation and a lumpy granular or hyaline change of the sarcoplasm. Occasionally the fiber changes resembled Zenker's degeneration.

The aforementioned morphologic changes, observed in part or completely in different animals, appear to constitute the morphologic pattern associated with absence of renal tissue. It is of extreme interest that the same pattern was observed in the group of animals not aided with the artificial kidney as well as in those whose survival was extended by in vivo dialysis.

In table 2 the frequencies of the specific lesions associated with this pattern are listed. It is to be noted that most of the types of lesions listed occur in both groups, but with a variation in frequency in the two groups. Moreover, the intensity of the lesions, as a general rule, became more pronounced as survival of the animals was extended.

The bronchial and bronchiolar smooth muscle and the pulmonary arteries and arterioles were closely studied in each animal. These structures were normal in appearance in all instances, thus conforming with established opinion and at the same time serving as an additional control of the observed changes in other tissues.

The smooth muscle of the splenic trabeculae displayed the same changes as smooth muscle elsewhere in animals surviving for longer periods. The central arteries of the splenic corpuscles, on the other hand, revealed no consistent changes.

Controls.—As controls, the tissues of 25 normal dogs were studied. All the tissues were normal in appearance, and in no instance were any of the lesions

TABLE 2.—*The Incidence of the Various Lesions Observed by Random Sampling in Bilaterally Nephrectomized Dogs* *

	Group 1 Not Subjected to Artificial Kidney		Group 2 Subjected to Artificial Kidney Once				Group 3 Subjected to Artificial Kidney Twice	
Period of survival, days	3 to 4+	5 to 5+	4 to 4+	5 to 5+	6 to 6+	7 to 7+	8 to 8+	9 to 9+
Dogs	14	13	4	6	8	13	4	7
Heart								
Subendocardial hemorrhage	21	46	25	16	25	70	25	57
Myocardial hemorrhage	35	38	25	30	50	38	37	43
Isolated degeneration	7	7	0	0	0	15	25	14
Necrosis	0	23	0	0	0	23	37	43
Arteriolar smudge	7	23	0	16	37	53	25	28
Stomach								
Hemorrhage	7	7	0	30	25	30	25	43
Necrosis	7	16	0	15	25	30	0	14
Arteriolar smudge	0	0	0	0	12	7	0	28
Smooth muscle degeneration	7	7	0	15	25	30	0	14
Intestine								
Hemorrhage	0	7	0	0	0	0	0	28
Necrosis	7	7	0	16	37	7	0	14
Arteriolar smudge	7	0	25	16	25	7	25	28
Smooth muscle degeneration	78	84	50	50	75	61	100	57
Esophageal and skeletal muscle degeneration	0	0	0	0	0	7	0	14
Urinary bladder								
Hemorrhage	0	7	0	0	0	15	25	0
Smooth muscle degeneration	7	14	0	0	12	7	25	0
Brain, hemorrhage	21	46	0	0	37	15	50	14
Spleen, smooth muscle degeneration	7	7	0	0	12	38	50	0

* Each number represents the percentage of all animals affected by the lesion listed in the column at the left.

described in the foregoing pages simulated. The control group included animals with intact kidneys subjected to the artificial kidney, animals receiving large doses of heparin, animals whose tissues were allowed to autolyze, and tissues from dogs succumbing to oligemic shock. In no instance were the arterial and cardiac lesions observed. However, in the case of an occasional animal that survived for 24 to 48 hours in shock after freezing of one hindlimb, the smooth muscle changes were demonstrated in the bowel, usually hyaline swelling and pyknosis in the form of the transverse bandlike arrangement. In connection with this finding, it is of interest that the animals had damaged kidneys and a large bulk of necrotic tissue in contact with the circulation. The intestinal smooth muscle changes, as already indicated, are the most common finding in bilaterally nephrectomized dogs and

have been observed as early as three days postoperatively. Moreover, intussusception has also been observed in dogs subjected to procedures leading to oligemia.

The ablated kidneys of each animal showed normal blood vessels and parenchyma. As already mentioned, an additional control was afforded by the lungs of each animal.

COMPARISON OF LESIONS OBSERVED IN BILATERALLY NEPHRECTOMIZED DOGS AND IN PERSONS DYING OF HYPERTENSIVE CARDIOVASCULAR DISEASE

The generalized muscle lesions occurring in the dogs that had undergone bilateral nephrectomy have also been observed in human cases of hypertensive cardiovascular disease and severe bilateral renal disease. Six such cases are being summarized here to emphasize the fact that the observations in the dog have a clinical counterpart.

In man, the medial necrosis of arteries and arterioles characteristic of hypertensive vascular disease has long been known. However, the less advanced hyaline swelling of sarcoplasm and pyknosis of nuclei of medial smooth muscle fibers have not been stressed. Conceivably the "hypertrophy of the media" described in the literature constitutes, at least in part, these degenerative alterations. Our observations indicate that the smooth muscle changes of the gastrointestinal tract, esophagus, urinary bladder, prostate gland and gravid uterus occurring in the course of the hypertensive state or severe bilateral renal disease in man are identical with the changes produced in the dog. The acute degeneration of myocardial and skeletal muscle has been encountered only a few times in human material, but when present it is identical with that observed in the experimental animal. However, it is not unusual to observe focal myocardial scars in hypertensive subjects without a satisfactory degree of coronary disease to account for such scarring. In addition, the prominence of heart failure during the course of clinical hypertensive cardiovascular disease cannot be adequately explained on the basis of simple cardiac strain secondary to elevation of arterial pressure.

CASE 1.—A white housewife aged 28 years was known to have been hypertensive four years previously, at which time she was pregnant. The pregnancy terminated in a stillborn infant at term. At the time of admission her complaints were blurring of vision, frontal headaches, nausea and vomiting, easy fatigability, swelling of the feet and ankles and dyspnea on exertion. Four days before admission these symptoms became exaggerated and she vomited a small amount of blood. One brother had died of hypertensive cardiovascular disease at the age of 28 years, and the father was known to have the same disease.

Physical examination revealed nothing except narrowing of the retinal arteries, without hemorrhages or exudates in the fundi and cardiac enlargement. The blood pressure was 250 systolic and 150 diastolic. The specific gravity of the urine was 1.020. Blood urea was 32 mg. and creatinine 1.6 mg. per hundred

cubic centimeters, and the phenolsulfonphthalein excretion was 60 per cent in two hours. Following a right sympathectomy (Smithwick procedure), the blood pressure was 210 systolic and 150 diastolic. The patient recovered from the operation satisfactorily and was discharged two weeks after the operation to return at a future date for sympathectomy of the opposite side. On the day following discharge the patient was readmitted because of pain of the left side of the chest, numbness of the left arm, abdominal pain and dyspnea. The blood pressure was 244 systolic and 140 diastolic, the pulse rate 110. The following day the patient died after a period of extreme dyspnea, tachycardia and hypotension.

At autopsy the pericardial sac was markedly distended with blood (cardiac tamponade). The hemorrhage was secondary to rupture of a dissecting aneurysm of the arch of the aorta. There were no intimal tears of the aorta. The heart was enlarged, weighing 500 Gm. The left ventricle was 2 cm. in thickness. Near the apex there were multiple linear subendocardial hemorrhages.

Microscopically, the media of the aorta showed advanced degeneration of the smooth muscle (hyaline swelling and pyknosis). Near the medial hemorrhage there were clear granular areas in the media (Erdheim's degeneration), with fibrosis of the media elsewhere. The heart showed definite hypertrophy.

In the abdominal viscera hyperemia was prominent, and there was moderate arteriolar sclerosis. The smooth muscle of the gastrointestinal tract showed hyaline swelling of the sarcoplasm and pyknosis. A random section of skeletal muscle revealed degeneration and necrosis of the muscle fibers. The kidneys displayed recent pelvic hemorrhages. Focal scars including hyalinized glomeruli and atrophic tubules were dispersed irregularly throughout the parenchyma. The main bulk of the renal parenchyma was intact. The proximal tubular segments revealed a prominent number of multinucleated epithelial cells.

Case 2.—A white man aged 60 years, of enormous proportions (weight over 300 pounds [136 Kg.]), had experienced orthopnea at night for three years and increasing shortness of breath on exertion. He had partaken excessively of food and alcoholic liquors for many years. On admission the patient was lethargic and had bubbling rales at the lung bases, an enlarged heart and massive edema of the lower extremities. The blood pressure was 200 systolic and 110 diastolic. The fundi demonstrated contracted arteries. The blood urea amounted to 32 mg. per hundred cubic centimeters. The patient responded poorly to therapy and died two days later.

At autopsy the heart was extremely enlarged, weighing 710 Gm. The average thickness of the left ventricle was 2.2 cm.; that of the right, 0.7 cm. The left ventricle had a prominently cupped cavity. The major portion of its subendocardial zone, especially in the apical region and the papillary muscles, showed grayish streaking of the classic tabby cat appearance. The coronary arteries demonstrated minimal atherosclerosis but were grossly patent throughout.

The gross tabby cat appearance was found microscopically to be due to areas of subendocardial degeneration and necrosis of myocardial fibers. The fibers demonstrated lumpy granular changes, focal transverse hyaline accumulations in the sarcoplasm, pyknosis and absence of nuclei of the type observed in the hypertensive dogs. The subendocardial connective tissue was thick and fibrous. Additional findings included marked myocardial hypertrophy, hyperemia, interstitial edema, focal capillary hemorrhages and degeneration of the smooth muscle of arteries and arterioles. Irregular microscopic scars were scattered throughout the myocardium. The apexes of the papillary muscles contained slight deposits of calcium salts. The aorta demonstrated fibrosis of the media and a decrease in smooth muscle fibers.

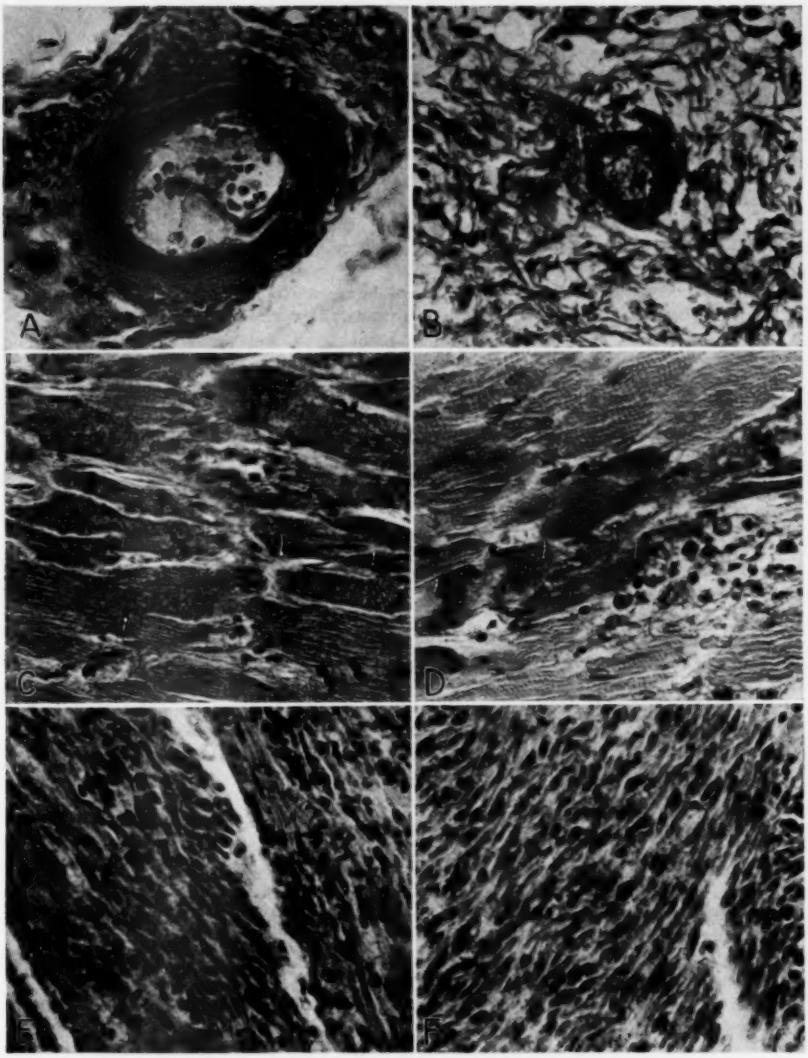

Fig. 5.—Lesions of blood vessels, heart and muscle as observed in human cases of hypertensive cardiovascular disease: *A* (case 5), arteriole in the submucosa of the ileum showing necrosis and smudging of the media identical with that observed in the dog as depicted in figure 2 *E*. There are also two lipid-containing macrophages in the intima which are elevating the endothelium. × 196.5.

B (case 6), arteriole near the capsule of the liver showing medial necrosis and smudging. × 196.5.

C (case 2), myocardium near the endocardium displaying degeneration and necrosis similar to that encountered in the dog (fig. 4 *C*). × 196.5.

D (case 1), isolated degeneration and necrosis of skeletal muscle fiber. × 196.5.

E (case 5), hyaline swelling and pyknosis of smooth muscle fibers of the circular muscular layer of the ileum. × 196.5.

F (case 4), smooth muscle layer of the esophagus showing marked hyaline swelling of sarcoplasm and pyknosis, as well as focal absence, of nuclei. × 196.5.

The right lung weighed 715 Gm.; the left 430 Gm. The main finding included hyperemia, edema and focal hemorrhages. The liver weighed 2,250 Gm. and showed advanced portal cirrhosis with fatty metamorphosis.

The combined weight of the kidneys was 570 Gm. The capsule stripped readily, and the surface was fairly smooth. Microscopically, there were small focal scars containing hyalinized glomeruli and atrophic tubules. The main bulk of the parenchyma was intact. The proximal segments contained a prominent number of multinucleated epithelial cells. Few hyalinized arterioles were seen, but an occasional arteriole showed medial necrosis. In the pelvis, hemorrhages were prominent, with several necrotic and smudged arteries and arterioles.

The smooth muscle of the gastrointestinal tract and the urinary bladder showed hyaline swelling and pyknosis. In the pancreas and the spleen arteriolar sclerosis consisted of intimal proliferation and medial hyalinization.

Case 3.—A 45 year old white man, a factory worker, first found to have hypertensive cardiovascular disease eight months prior to admission, entered the hospital complaining of throbbing headaches, nosebleeds, blurring of vision, shortness of breath, "asthma," polyuria and nocturia. Six months previously he had suffered a "stroke," which was followed by weakness of the left side. Four days before admission, gross hematuria developed. Physical findings included enlargement of the heart, determined by percussion, and a loud apical systolic murmur. The blood pressure was 242 systolic and 150 diastolic. Ophthalmoscopic examination revealed hemorrhages, exudates, papilledema, arteriovenous nicking and narrowing of the arteries. The blood urea amounted to 71 mg. and creatinine to 3.4 mg. per hundred cubic centimeters. An excretory urogram was normal. After unilateral sympathectomy (Smithwick procedure), the blood pressure dropped to 90 systolic and 70 diastolic; the patient became unresponsive, and death followed on the second postoperative day.

At autopsy the heart weighed 720 Gm., with the left ventricle enlarged to 2 cm. in thickness. A roentgen study of the coronary arteries by Schlesinger's technic revealed no major obstruction, and grossly the coronary arteries were free of atherosclerosis. Microscopically, the hypertrophied myocardium displayed scattered irregular scars, hyperemia and interstitial edema. Branches of the coronary artery revealed hyaline swelling of sarcoplasm and condensation of nuclei of the smooth muscle of the media.

The lungs weighed 700 Gm. and showed hyperemia, edema, focal hemorrhages and pigmented macrophages. The liver weighed 2,300 Gm. and was hyperemic, as were also the kidneys, which together weighed 360 Gm. Their surface was moderately granular. Microscopically, there were multiple scars and areas in which atrophy of the parenchyma alternated with hypertrophy. The larger arteries revealed the intimal thickening of arteriosclerosis and hyaline swelling and pyknosis of the medial smooth muscle. Hyalinized arterioles were common. Focal necrosis of the media of arteries and arterioles with eosinophilic smudging was also encountered.

The smooth muscle fibers of the gastrointestinal tract, esophagus, aorta, urinary bladder and prostate gland had undergone a striking degree of hyaline thickening of the sarcoplasm and nuclear condensation and distortion. A periadrenal artery revealed necrotic smudging of the media.

Case 4.—A 67 year old white man was unconscious on admission, at which time his blood pressure was 260 systolic and 150 diastolic and the spinal fluid grossly bloody. The patient had suffered two "strokes," one and five years before admission. The patient died the day following admission.

At autopsy the heart weighed 375 Gm., with the left ventricle 1.5 cm. in thickness. The coronary arteries were patent. Multiple irregular scars were seen in the microscopically hypertrophied myocardium.

The lungs were moderately emphysematous with focal capillary hemorrhages. The smooth muscle of the gastrointestinal tract and the urinary bladder displayed a striking degree of hyaline swelling of sarcoplasm and pyknosis and distortion of nuclei. The kidneys were small and granular, weighing together 200 Gm., and displayed areas of focal scarring and marked arteriolar hyalinization. The smooth muscle fibers of the media of the larger arteries were thickened and hyalinized. There was a hemorrhage in the left frontal lobe, which had ruptured into the subarachnoid space.

CASE 5.—A 47 year old Negro was alleged to have been well until the day before admission when severe headache developed while he was at work and he became unconscious. On admission the blood pressure was 220 systolic and 180 diastolic. Th spinal fluid was bloody, and there was paralysis of all the extremities except the right hand. The blood pressure subsequently fell to 170 systolic and 140 diastolic; the patient became cachectic despite the fact that he was fed by tube a high caloric diet, and death followed forty-eight days after his admission.

At autopsy the heart weighed 470 Gm., with the left ventricle 2.5 cm. in thickness. The coronary arteries were grossly patent. There was fibrous thickening of the endocardium with hypertrophy of the myocardial fibers. In the myocardium arterial branches demonstrated degeneration and focal necrosis of smooth muscle with early smudging.

The arterioles of the abdominal viscera were hyalinized and thickened. The smooth muscle of the gastrointestinal tract, urinary bladder and prostate gland displayed marked hyaline swelling and pyknosis of the fibers. The kidneys, which together weighed 435 Gm., had a smooth surface but microscopically showed areas of scarring. In both the proximal and the distal segments there were many multinucleated epithelial cells. The smooth muscle of the larger arteries was degenerated. In the brain a hemorrhage was present in the right basal ganglions.

CASE 6.—A 49 year old white man suddenly experienced nausea, vomiting and left-sided clonic convulsions. One year before, he had been hospitalized for myocardial infarction and cerebral embolism. On admission there was intense tachycardia and the blood pressure was 150 systolic and 100 diastolic. Subsequently the blood pressure was observed to be 118 systolic and 80 diastolic. There was evidence of myocardial damage. The patient appeared to improve gradually but died suddenly nineteen days after admission.

At autopsy the heart, which weighed 450 Gm., contained a large recent infarct of the left ventricle with a mural thrombus. The descending branch of the left coronary artery was occluded by a recent thrombus near its origin. The myocardial fibers were hypertrophied and contained scattered scars.

The lungs showed hyperemia and multiple confluent parenchymal hemorrhages. The liver weighed 1,320 Gm. and had many necrotic arteries and arterioles. These vessels showed the eosinophilic smudging of the media observed in the dog. The pancreas contained both hyalinized arterioles and necrotic arteries and arterioles.

The left kidney weighed 270 Gm. and was surrounded by a hemorrhagic envelope 0.4 cm. in thickness. On section this kidney had multiple infarcts which had destroyed 75 per cent of the renal substance. The right kidney weighed 280 Gm. Its capsule was densely adherent and the surface granular. There

was a small hemorrhage in the upper portion of the pelvis. Microscopically, infarcts were identified in the left kidney. The right kidney had multiple scars containing atrophic parenchyma. Arteriolar sclerosis with hyalinization of the entire wall was common. In the hemorrhagic area in the pelvis were several small arteries displaying necrosis and eosinophilic smudging of the media.

We believe that this patient primarily had coronary artery disease with myocardial infarction. The infarcts of the left kidney, due to emboli from the mural thrombus, plus nephrosclerosis of the right kidney, apparently so depleted the amount of functioning renal tissue as to be followed by necrotizing lesions of arterioles in the viscera. The findings in this patient are comparable to those observed in the nephrectomized dog.

COMMENT

The hypertension that developed in bilaterally nephrectomized dogs obviously could not have resulted from elaboration of renal pressor substances. It must be concluded, on the other hand, that the kidney normally exerts a function concerned with the maintenance of the normotensive state. In order for bilaterally nephrectomized animals to manifest hypertension of a significant degree, two conditions must be satisfied; namely, the general condition of the animal must be relatively good, and the survival period must be extended to five days or more. In the present study these requirements were attained by depriving the animals of electrolytes and by the periodic application of the artificial kidney.

The present study has demonstrated that survival of nephrectomized animals is limited as a result of the development of widespread lesions, even when the animals are subjected to in vivo dialysis. The alterations observed in arteries and arterioles satisfy the established criteria for the changes occurring in hypertensive cardiovascular disease. The observed widespread lesions involved predominantly muscular tissue. In the smooth muscle tissue of the arteries the changes appeared to undergo a transition from degenerative alteration to necrosis. The degenerative changes were characterized by an eosinophilic hyaline swelling of the sarcoplasm and pyknosis of the nuclei. The necrosis was characterized by eosinophilic smudging. The smudged media may spread toward the lumen or toward the adventitia. With the former, narrowing or sloughing into the lumen occurs, the slough at times giving rise to plugging of the capillaries. The spread toward the adventitia imparts to the vessel an accentuated thickness. This vascular necrosis was distinctly segmental in distribution whereas the degenerative changes assumed a more widespread distribution. Normal-appearing vascular segments could be identified in all cases.

Degeneration and necrosis of heart muscle reflected severe injury of this tissue. The fact that this change occurred in isolated fibers indicates that the muscle fiber was altered primarily and was not affected

merely as a result of the vascular changes. The severe damage of the heart might be considered to have interfered subsequently with the attainment of maximal rises of blood pressure.

Other muscular structures involved by the process included the gastrointestinal tract, which was particularly affected. Here the lesions resembled those of the blood vessels in their early phases and those of the heart. A high incidence of intussusception was associated with these muscle changes, and it seems highly probable that there is a causal relationship between these findings. Intussusception was also observed by Winternitz and associates [4b] and by Goldblatt [1] in dogs with high blood pressure.

Other organs containing smooth muscle were also involved. The urinary bladder, which presumably was in a nonfunctioning state, demonstrated these changes, but to a lesser degree. The involvement of skeletal muscle, although definite, was less widespread.

Study of human tissues, as illustrated in the reported cases, has demonstrated the occurrence of lesions identical with those encountered in the dog with hypertensive vascular disease following bilateral nephrectomy. The degeneration and necrosis of the smooth muscle of arteries and arterioles has been a common finding. Almost equal in frequency have been the similar changes observed in the gastrointestinal tract. Only isolated examples of the acute degeneration and necrosis of myocardium and skeletal muscle have been seen in 100 cases of hypertensive vascular disease which we have examined. However, myocardial fibrosis in the absence of advanced disease of the coronary arteries is common and reflects, we believe, the existence of primary myocardial damage, which accounts for the high incidence of congestive heart failure in cases of hypertensive cardiovascular disease.

The degeneration of smooth muscle has been encountered in both the benign and the malignant forms of hypertensive cardiovascular disease. In the malignant form the necrosis with eosinophilic smudging occurs. As in the experimental animals, the latter change appears to be a more advanced form of the hyaline swelling and pyknosis. Lesions of smooth muscle have also been observed in bilateral renal disease other than hypertensive cardiovascular disease. Outstanding in this group has been glomerulonephritis, either the acute fulminant proliferative type or the chronic destructive type. Also, occasional patients, not exhibiting hypertensive cardiovascular disease clinically but having generalized arteriolar sclerosis and an enlarged heart, have been shown to have degeneration of the smooth muscle of the gastrointestinal tract. Thus, the smooth muscle changes seem to be a counterpart of the arteriolar disease which also results from involvement of this tissue in the blood vessels.

Under certain conditions the smooth muscle changes, particularly those involving the gastrointestinal tract, have been observed in the absence of a terminal elevation of blood pressure, namely, after prolonged peripheral circulatory failure and in the aged with generalized arteriolar sclerosis. In the former condition there is severe renal failure which simulates nephrectomy. In the latter there may be hypertrophy of the heart at the time of autopsy, and these persons may be considered to have had a period of elevated blood pressure, which has receded. In the absence of cardiac hypertrophy these changes in the smooth muscle occur particularly in the aged with generalized arterial and arteriolar sclerosis.

A common finding in subjects of high blood pressure, both young and old, has been the presence of multinucleated cells in the proximal segment of the renal tubule. This alteration has been observed in patients having an adequate renal excretory function shortly before death. It is conceivable that this nuclear proliferation [18] is a reflection of functional alteration of the tubular cells

In 4 of the 6 human cases reported in this study, severe vascular hypertension was associated with generalized lesions of muscle but not with extensive renal arteriolar sclerosis, in keeping with the observations of Castleman and Smithwick.[19]

SUMMARY AND CONCLUSIONS

In dogs bilateral nephrectomy resulted in the development of hypertensive cardiovascular disease when the animals were maintained in a relatively good state of health for a sufficiently long period. At autopsy these animals displayed the vascular lesions commonly ascribed to "malignant hypertension." In addition, the disease process affected muscle tissue throughout the body. The alterations in muscle tissue were of a degenerative and necrotic type and were identical with those seen in the human being dying of hypertensive cardiovascular disease. A detailed study of these lesions observed in the experimental animal and in the human patient is presented.

18. We have designated this change as "tubular nucleosis" in the analogy to the "nucleosis of skeletal muscle." Harman and Hogan (Arch. Path. **47**:29, 1949) have described it as an accumulation of multinucleated epithelial cells occurring in conditions in which hypertension is notable.

19. Castleman, B., and Smithwick, R. H.: New England J. Med. **239**:729, 1948.

PERITONEAL PSEUDOMYXOMA

A Report of Four Unusual Cases

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SINCE Werthe[1] first described peritoneal pseudomyxoma in 1884, approximately 500 cases have been reported; in better than four fifths of these the condition was thought to be of ovarian origin. It is the purpose now to describe 3 cases in which it was of appendical origin, with unusual findings in the patients, who were all males. A fourth case, in which the patient was a woman with an unusual history, is included.

The disease is relatively rare. Weaver[2] reported that in a series of 256 cases of mucocele of the appendix, the mucocele was associated with peritoneal pseudomyxoma in 0.11 per cent. He also reported a series of 6,223 appendectomies with only 7 mucoceles, of which 1 alone had given rise to peritoneal pseudomyxoma. In over 8,100 consecutive autopsies at Montefiore Hospital since 1917, there were only 3 that disclosed this disease. To these 3 may be added a fourth, diagnosed at laparotomy; there was no autopsy in the case. In this series of autopsies, only 3 unruptured mucoceles of the appendix were noted.

The commonly accepted genesis of the disease, described first by Olshausen,[3] is that a cystic dilatation of the appendix (mucocele) occurs from occlusion, probably the result of inflammation. The mucocele then ruptures on the peritoneum, where some of the lining cells are implanted, which in turn give rise to cysts, and these, with the original mucocele, are thought to be the source of a massive "seeding" of the peritoneum with myriads of cysts. Along with this process, there is apparently a reactive fibrosis which results in thickening of the peritoneum and of the cyst walls.

The question how the cysts arise is not settled. The cellular implantation theory is favored. Koerner[4] suggests that peritoneal pseudomyxoma, secondary to ovarian cystadenoma, is secondary to implantation of appendical cells from a ruptured mucocele or an inflamed

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From the Laboratory Division, Montefiore Hospital.

1. Werthe, cited by Krivsky.[18]
2. Weaver, C. H.: Am. J. Surg. **36**:523, 1937.
3. Olshausen, R.: Ztschr. f. Geburtsch. u. Gynäk. **11**:238, 1884.
4. Koerner, T.: Deutsche Ztschr. f. Chir. **237**:158, 1932.

and ruptured appendix on a freshly ruptured ovarian follicle bed (corpora hemorrhagica) (case 4). Of more importance from a diagnostic point of view is the question of cancer, since in the 4 cases reported here, surgical specimens proved difficult to evaluate and were usually reported as mucogenic adenocarcinoma. This problem will be discussed further.

HYPOGLYCEMIA IN PERITONEAL PSEUDOMYXOMA

CASE 1.—B. C. was a 46 year old white shopkeeper with an unremarkable history. On his first admission, June 24, 1943, his chief complaints were postprandial heartburn, recent loss of 10 pounds (4.5 Kg.) and gradual increase in the girth of his abdomen for about three months. There was moderate distention of the abdomen, and large irregular masses were palpable across the upper part of the abdomen, with shifting dulness in both flanks. A smooth, firm, orange-sized mass was felt 5 cm. above the anus in the anterior rectal area, but it was not fixed. There was moderate pitting edema of both legs. All roentgen aspects of the gastrointestinal tract were within normal limits. The laboratory results were not remarkable. Paracentesis yielded 3,800 cc. of a clear yellow fluid containing bits of mucoid material. Concentration and cell block examination of this fluid failed to reveal tumor cells. A laparotomy disclosed "generalized carcinomatosis involving the entire omentum, peritoneum, and surface of the liver." A biopsy of the omental mass was reported as revealing colloid carcinoma. During the next four years repeated paracenteses were necessary, each yielding an average of 4,000 cc. of yellowish fluid containing gelatinous material. There was a gradual loss of weight with continued distention of the abdomen, but the patient was otherwise without complaints.

For six weeks prior to the second admission, May 1, 1946, the abdominal swelling had increased and there was diffuse abdominal pain. The swollen abdomen had prominent venous collaterals over the surface. There was moderate pitting edema of the legs. Fine moist rales were heard over both lung bases. A huge, firm, nodular, irregular mass occupied the upper right abdominal quadrant and extended down to the iliac crest and to the left as far as the midhypochondrium. Shifting dulness was present in both flanks. The mass in the rectal area had increased to the size of a grapefruit.

The hemoglobin level was 7.0 Gm. per hundred cubic centimeters of blood; the red blood cell count was 2,600,000; the white cell count, 5,700, with a normal differential count. At first test the fasting blood sugar amounted to 36 mg. per hundred cubic centimeters; at a repeated test it amounted to 38 mg. Blood urea nitrogen was 17.7 mg., blood cholesterol 12 mg. and serum protein, 4 Gm. per hundred cubic centimeters, with the albumin-globulin ratio 1.0. Cephalin flocculation was 4 plus; thymol turbidity, 15 units.

Two weeks later the patient lapsed into coma. During the reaction the blood sugar was reported as 50 mg. per hundred cubic centimeters. The patient was given 50 cc. of 50 per cent dextrose solution intravenously and recovered in a few minutes. He had complete retrograde amnesia for the event. Two similar episodes occurred on the withholding of breakfast, each preceded by sweating, chilliness and generalized coarse tremors. Because of the emergency of the reaction, the blood was not tested for sugar, but the patient was given 75 cc. of 50 per cent dextrose solution intravenously and within two minutes regained consciousness. Altogether

the patient had five such episodes over six weeks. The shock episodes ceased as abruptly as they had begun after it was no longer necessary to withhold food for diagnostic studies.

A biopsy of a point where some of the mucinous material had apparently infiltrated the subcutaneous tissue of the abdomen, along the old operative site, was reported again as revealing mucinous adenocarcinoma with marked secretion of mucin. The patient was discharged as improved Oct. 30, 1946, and remained fairly free of symptoms until two weeks before his third admission, March 5, 1947, when he began to vomit a coffee-ground material and experienced severe crampy abdominal pain. On admission his blood pressure was unobtainable and coarse moist rales were heard over the left side of the chest posteriorly. The patient was semicomatose and slightly cyanotic. The results of an abdominal examination were similar to those on previous admissions. He failed to respond to treatment and died twenty hours after admission—approximately four and one-half years after the onset of the abdominal swelling. The clinical impression at the time of death was intestinal obstruction and pneumonia. No laboratory studies were made on this admission.

Autopsy (nine hours after death).—The body was markedly emaciated, with a greatly distended abdomen. The peritoneum was infiltrated throughout with confluent pinhead to pea-sized cysts and large grapelike cysts containing a thick, opaque, whitish gray gelatinous material, some of which lay free in the 5,000 cc. of turbid brownish fluid in the cavity. This fluid contained bits of necrotic tissue, fibrin and cellular debris. Over portions of the intestines was a grayish brown, friable membrane. Cysts were present on all the peritoneal surfaces. The greatest bulk of gelatinous material occupied the mesocolon, the terminal 10 cm. of the mesentery and the serosa of the ileum. A large grapefruit-sized mass of confluent cysts occupied the pelvis.

The appendix was thickened, measuring 6 to 7 mm. in diameter near the distal end, where the lumen was occluded. Within the lumen, near the cecal opening, there was some free gelatinous material, proximal to which the lumen was again occluded. At about the central portion the lumen was moderately dilated and contained gelatinous material. A portion of the wall was lined by the gelatinous masses and communicated with an eroded section of the cecum adjacent to the appendical orifice. The entire appendix was buried in the mass of cysts. Partial compression of both ureters had resulted in moderate dilatation. Except for patchy bronchopneumonia of the lower lobe of the left lung, all other organs were normal.

Microscopic Examination.—All sections of intestine showed numerous irregular mucin-containing spaces adherent to, or within, the serosa. Sections of the dilated proximal portion of the appendix (fig. 1) were characterized by an atrophic mucosa, devoid of lining cells, with but a few small glands in a thin submucosa, in which there was moderate round cell infiltration. In places the muscularis had been ruptured and pushed aside, and small cystic spaces formed most of the wall. No lymphoid follicles remained. The occluded portion of the appendix showed thickened and fibrotic walls, with moderate round cell infiltration of all layers, and the mucosa and submucosa were replaced by fibrous tissue.

The cystic masses contained mucinous material staining with Mayer's mucicarmine. An occasional cyst was lined by a single layer of low cuboidal cells containing basal hyperchromatic or reticulated nuclei and prominent nucleoli and in places showed a gradual progression from flattened to cuboidal and columnar cells (fig. 2). No mitotic figures were seen. Most cysts were unlined, and occa-

sionally the lining cells lay free within the lumens. The cysts were separated by fairly thick fibrous tissue septums containing engorged capillaries and a few lymphatic channels. In some areas the septums were hyaline. A few granules of blood pigment and phagocytes were present. The surgical specimens were essentially similar.

The liver (fig. 3) contained numerous dilated sinuses with necrotic cells. In some cases fibrocytes were growing into the necrotic zones. The sublobular hepatic veins were engorged and the central veins slightly dilated. These findings suggested a severe increase in hepatic vein pressure, with resultant distention of sinusoids, disruption of cells and hemorrhage.

Case 2.—J. S. was a 51 year old white cloth cutter. His past history was not remarkable except for "yellow jaundice" in 1940-1941, with complete recovery.

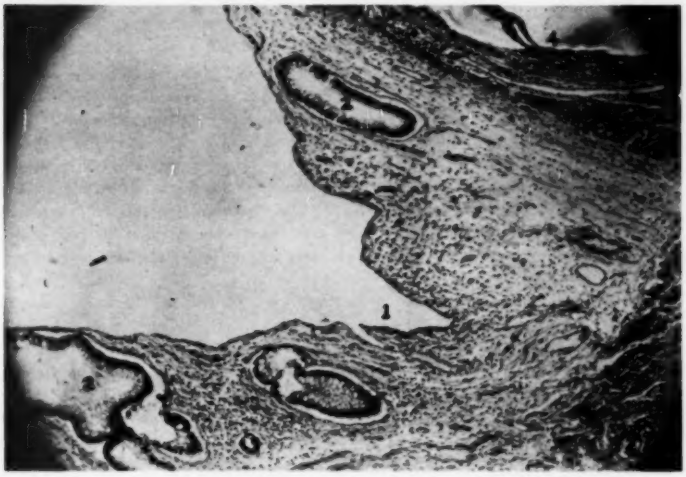

Fig. 1 (case 1).—Appendical lumen showing: (*1*) atrophic mucosa devoid of lining cells; (*2*) few small submucosal glands (these were the only remaining glands); (*3*) thinned out muscularis; (*4*) cystic space infiltrating muscularis and serosa; × 58. Note small cell infiltration of all layers.

He was first admitted to another hospital, Dec. 12, 1945. The chief complaint was swelling of the abdomen for nine months. Two paracenteses had been necessary in the previous three months. The abdomen was markedly rotund, with a fluid wave over the lower portion. No organs were palpable. The hemoglobin was 11.3 Gm.; the red blood cell count, 3,940,000; the white cell count, 10,000, with a normal differential count. The blood sugar was 60 mg. per hundred cubic centimeters. The diagnosis was "unlisted tumor of the abdomen." The patient was readmitted to the same hospital five times for paracenteses. A blood sugar level taken during this period was 35 mg. per hundred cubic centimeters. He received a number of transfusions for hypochromic anemia. At laparotomy,

June 14, 1946, the following notation was made: "The abdominal cavity was filled with a large amount of gelatinous material; the intestines were matted together, and the individual organs were not recognizable, as they were covered with

Fig. 2 (case 1).—Lining cells of a small cyst occurring in a myxomatous matrix; × 545. Note single cuboidal to columnar epithelium, hyperchromatic nuclei and prominent nucleoli and secretory granules.

gelatinous masses. No surgical therapy was thought possible." A biopsy of the omentum was reported as revealing "mucoid degeneration of the connective tissue (pseudomyxoma peritonei?)."

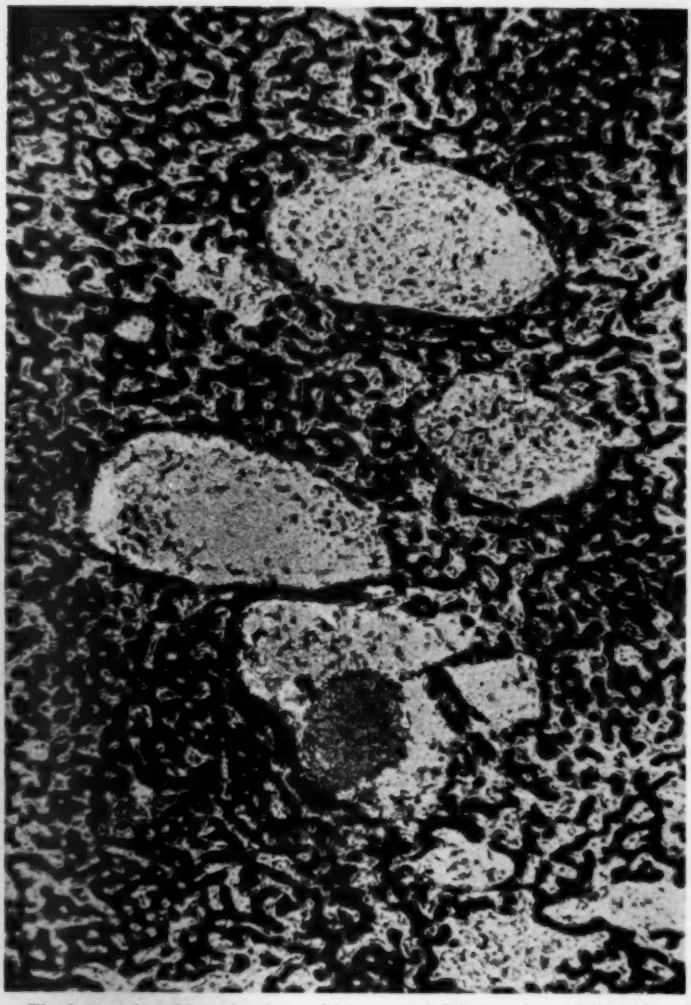

Fig. 3 (case 1).—Liver showing multiple areas of disintegration and disruption of cords, blood pools with necrosis of adjacent cells, and dilatation of sinusoids; ×83.

Fig. 4 (case 2).—Gelatinous material showing matrix with (*1*) small active cyst and (*2*) lining of larger adjacent cyst (see description in text); × 255.

The last admission was on Sept. 16, 1946, for severe abdominal distention. A fluid wave was present in both flanks and firm irregular masses were palpated across the midabdomen. There was a firm, smooth, orange-sized mass anterior to the rectum. There was moderate pitting edema of both legs.

The hemoglobin was 6.4 to 9.5 Gm. despite repeated blood transfusions; the total serum protein was 4.9 to 5.7 Gm. per hundred cubic centimeters, with the albumin-globulin ratio 0.9 to 1.5. The blood sugar varied from 65 to 95 mg. and total cholesterol from 134 to 221 mg., per hundred cubic centimeters. The cephalin flocculation test was negative. Retention of sulfobromophthalein was 48 per cent in ten minutes.

Repeated paracenteses and blood transfusions were necessary. On a high calory, high protein diet the edema of the extremities subsided. On Feb. 3, 1947, a second laparotomy was done. "Multiloculated cysts filled with gelatinous material occupied the greater peritoneal cavity. The distal end of the appendix ended in such a cystic cavity, and the appendical lumen was filled with gelatinous material. A portion of the cystic mass in the omentum was evacuated, and the appendix and the cyst in which it ended were removed." On the ninth postoperative day pneumonia developed. The patient died nine days later—approximately two and a half years after he had first noticed the abdominal swelling. Unfortunately, no glucose studies were made. Autopsy was not permitted.

Report of Surgical Specimens (Dr. S. H. Rosen).—"The specimens were an intra-abdominal cystic mass and the appendix. A cross section of the solid portion of the appendix showed the lumen obliterated by loose fibrillary connective tissue. The propria and the muscularis were thickened by fibrous tissue with marked swelling and separation of the fibers by a homogeneous granular pink-staining material (mucus). There was slight cellular infiltration of all layers. There were large and small intercommunicating irregular spaces filled with a homogeneous granular pink to blue-staining material in the mesoappendix. These spaces were separated by connective tissue septums, which were somewhat vascular and infiltrated in places by inflammatory cells. In some areas the septums were dense and hyalinized. Focal hemorrhage and blood pigment were seen in some areas. The lining (fig. 4) of the spaces varied from none to single layered, flattened cuboidal cells, and in other areas the cells varied from single layered cuboidal to columnar cells. These cells had acidophilic cytoplasm, frequently vacuolated, and round central or basal hyperchromatic nuclei, with prominent nucleoli. No mitotic figures were seen.

"A section of the cystically dilated appendix showed a thin wall with swelling, degeneration, and, in places, edema or mucus replacing the muscularis. Slight polymorphonuclear and small round cell infiltration was present. No normal mucosa or lymphoid tissue was seen. The lumen was lined with a single layer of columnar cells similar to those described lining the cysts. A small amount of mucus was present in places on the inner surface. A section of the omental mass showed irregular cystlike spaces exactly similar to those already described." (A review of the biopsy specimen taken at the first laparotomy revealed similar findings.)

SPLENIC INFARCTION AND RUPTURED MUCOCELE OF THE APPENDIX

Case 3.—A. L. was a 53 year old white laborer. His past history was not remarkable. The first admission was on Feb. 15, 1927, with the chief complaint swelling of the abdomen for one month. The abdomen was swollen and rotund,

with a fluid wave in both flanks, a palpable mass of grapefruit size in the left mid-abdominal region and a sliding inguinal hernia of the left side. The hemoglobin was 70 to 80 per cent; the white blood cell count, 2,800 to 3,600, with a normal differential count. An inguinal hernioplasty was made through the open hernial sac. The omentum was a mass of tumors and the peritoneum nodular. Appendectomy was done and a biopsy specimen taken from the omental mass. The pathologist reported metastatic carcinoma and appendicitis.

During the next four years the patient was hospitalized four times with continued swelling of the abdomen and occasional pain in the left upper quadrant. The mass continued to increase in size. There was intermittent diarrhea, and moderate edema of the ankles developed. Repeated paracenteses were necessary, and on two occasions cell blocks of the concentrated abdominal fluid were reported to contain "tumor cells." Gradually dyspnea developed with general weakness, loss of weight, pain in both lower extremities and episodes of nausea and regurgitation. At laparotomy, Feb. 11, 1930, the following notation was made: "Large quantities of thick mucoid material were present over the entire peritoneal surface. Intestines and omentum were studded with gelatinous grapelike tumor, and most of the omentum was a thick gelatinous mass. Inoperable."

The final admission was on May 26, 1931. There was no change except that the patient was more emaciated. At the third laparotomy, June 11, this notation was made: Abdominal findings similar to those found on the second exploration, with the addition of a grapefruit-sized mass in the upper left quadrant. Inoperable." Two days after the laparotomy the patient had severe epigastric pain, rapid pulse and fever. He died four and a half years after the onset of his illness, with intestinal obstruction and possible perforation.

Autopsy (Dr. S. H. Rosen).—The body was that of a fairly well developed, emaciated white man with a large, rotund abdomen, in the left upper quadrant of which a grapefruit-sized mass was palpable. The peritoneal cavity contained 5,000 cc. of turbid brownish fluid with numerous yellow and gray friable shreds and dark green flecks. All the peritoneal surfaces were studded with irregular nodules from pinhead to hazelnut size. Some were translucent and composed of firm, thick mucoid substance; others, of firm, opaque, grayish white tissue, and others, of both elements. In places, especially around the descending colon, small nodules were massed in clusters like bunches of grapes. Over the entire parietal peritoneum and over the serosa of the stomach and the large and small intestines they were so closely packed as to form a continuous nodular sheet. Large retroperitoneal cystic masses were present in the region of the descending colon, cecum and appendix (the last having been amputated). Another such mass was found in the rectovesical area. The omentum was greatly thickened and irregular because of the gelatinous and opaque tissue which infiltrated it. The coils of intestine were matted together with a friable grayish and yellowish exudate. In a loop of jejunum was a round perforation about 1 cm. in diameter, the edges of which were smooth, soft and reddish green. The plastic exudate appeared more abundant in this area.

The spleen was encased in a thick mass of grayish white opaque, gelatinous material, which completely surrounded it except at the upper pole. This tissue was 3 to 6 cm. in thickness and formed an oval mass, measuring 25 by 16 by 13 cm. It was firmly adherent to the parietal peritoneum. On section, about two thirds of the spleen was found to be softened, almost mushy in consistence, and saturated with blood. The markings were obliterated. It was an obvious hemorrhagic infarction. The splenic veins were compressed and occluded near

the hilus by the encasing tumor mass. The entire surface of the liver was covered with large masses of gelatinous tissue which in places extended through the capsule into the parenchyma. Besides the perforation, there was an annular stricture of the ileum about 8 cm. from the ileocecal valve. The site of the amputated appendix was marked by an opaque whitish thickening of the wall of the cecum with adherent masses of gelatinous material. All remaining organs were normal.

Microscopic Examination.—Numerous sections of the tumor masses showed a greater or lesser accumulation of connective tissue septums, surrounding cystic spaces lined by a single layer of cuboidal to columnar cells. These cells were of medium size, with moderately dense acidophilic cytoplasm and large vesicular or hyperchromatic nuclei and prominent nucleoli. Infiltrating into some of the muscle layers from the serosa of the intestines along the connective tissue septums were a few of these cells forming groups and cords and occasionally pseudoalveoli. In an occasional area there was piling up of the nuclei with loss of cell borders. No mitotic figures were seen. Isolated cells with a tendency toward vacuolation were present. The stroma was loose and fibrillar, with a pale bluish myxomatous appearance.

Sections from portions of the spleen showed sinuses distended with red blood cells, and moderate fibrosis in scattered areas. There was focal necrosis of many of the malphigian bodies. Trabeculi were thickened. In other areas the splenic structure was destroyed and replaced by an almost solid sheet of large, pale mononuclear cells (reticulum and endothelial cells), many of which contained blood pigment. Scattered among these cells were numerous red blood cells and a few lymphocytes.

All other organs were normal.

Case 4.—E. T., a housewife, came to the hospital first in 1930 at the age of 46 because of vaginal bleeding. Hysterectomy and oophorectomy on the left were followed by cessation of bleeding and mild hirsutism. The patient remained well until January 1940, when she began to complain of enlargement of the abdomen. A paracentesis in February 1940 yielded a large amount of gelatinous material. When hospitalized in April 1940 she had a distended abdomen with a fluid wave and a large firm mass in the pelvis. There was a moderate anemia. At laparotomy, April 17, a large amount of thick jelly-like material escaped. A large cystic mass filled the entire pelvis. There were innumerable small cysts in the omentum and peritoneum, and sections of cyst wall showed "papillary pseudomucinous cystadenocarcinoma of the ovary."

During the next six years the patient had twenty-two admissions for paracentesis but remained otherwise in fairly good health, complaining only of slight but continuous enlargement of the abdomen and the need for repeated paracenteses. When admitted for the twenty-second time, March 12, 1946, the abdomen was so enlarged that roentgenograms of the chest and an intravenous pyelogram were difficult to interpret.

At laparotomy, April 19, the surgeon removed an immense cystic mass by sharp and blunt dissection, separating it from the bowels and the lateral pelvic walls. Two elongated cystic nodules attached by pedicles to the mesentery were also removed. The patient made an uneventful recovery, and following moderate high voltage radiotherapy there was no recurrence of the mass or the ascites.

July 21, 1947, the patient was suddenly seized with severe colicky epigastric pain which began in the right upper quadrant and was transmitted across to the left upper quadrant of the abdomen. When she was admitted to the hospital

two days after the onset of pain, tenderness was present in all quadrants of the abdomen, with no spasm, distention or increased peristalsis. No masses were noted. Her temperature ranged from 101 to 103 F. There was occasional vomiting. A flat roentgenogram of the abdomen showed some fluid levels in the small bowel. No definite diagnosis was possible. Five days after admission her condition changed rather quickly as her pulse became fast and thready and tenderness developed in the right lower quadrant and costovertebral angle. A diagnosis of peritonitis was made, and she was treated with penicillin and streptomycin, but died six days after admission—one year and three months after the removal of the abdominal mass and seven years after the beginning of her illness. The patient had moderate hypertensive cardiovascular-renal disease and was a chronic complainer of fibrillation, but at no time was she known to have had cardiac decompensation and there was no sign of cardiac failure.

Autopsy (Dr. E. M. Blondheim).—The body was that of a well developed, well nourished woman of about 63 years of age. Except for two abdominal scars, there were no abnormalties externally. The parietal peritoneum was markedly thickened and brownish. About 2,000 cc. of a thin purulent yellowish fluid was present, and the peritoneum was covered with a greenish fibropurulent exudate. On the under surface of the diaphragm and between the capsule of the spleen and the surrounding tissue there were moderate numbers of pinhead-sized red and blue jelly-like implants. The serosal surfaces of the intestines were covered with a fibrinopurulent exudate. Extending up the medial border of the cecum was the appendix. It was attached to the cecum laterally by fibrinous adhesions and covered with a thick fibrinous-purulent exudate and some fecal material. The latter was oozing out of a punched-out pinhead-sized perforation near the distal end of the anterolateral aspect. The wall was somewhat thickened and fibrotic throughout, and the lumen was not occluded. The pelvic organs were absent, and the pouch of Douglas was obliterated by fibrous tissue. The left side was somewhat deeper than the right and contained a shaggy purulent greenish exudate. The remaining abdominal organs showed no abnormalities.

Microscopic Examination.—Sections through the capsule of the spleen at the site of the jelly-like implants revealed islands of a myxomatous material similar to Wharton's jelly. Similar myxomatous tissue was found on the under surface of the diaphragm. A thick layer of edematous fibrous tissue with round cell infiltrate and small deposits of calcium lay beneath the muscularis of the appendix. The lumen was dilated and the mucosal epithelium absent. In one area the mucosa was represented by a few poorly preserved papillary processes in which were a few pale-staining cells with prominent vacuoles. The bases of some of the crypts were recognized and consisted of columnar cells with basal nuclei and occasional goblet cells. The serosal surface showed edematous and inflamed fibrofatty tissue with a surface layer of fibrin and in this region were a few islands of degenerated myxomatous tissue, already described. The other organs were not remarkable.

Review of Surgical Material (Pelvic Cystic Mass—April 19, 1946).—A large irregular mass, measuring 27 by 14 by 7 cm., had coarsely nodular surfaces, owing to multiloculated cysts, which were filled with a glairy greenish gelatinous fluid. The cysts varied from a few millimeters to 7 or 8 cm. in diameter, and the walls varied from paper thin to 5 or 6 mm. The walls consisted of gray fibrous tissue with a smooth lining, and the larger walls contained in some areas cysts with mucoid material. Two smaller ovoid cystic masses were present (omental biopsies).

Microscopically, the tumor consisted of large irregular branching tubules and of small and large cysts. The tubules were lined by one to several layers of tall columnar cells. Some of the cysts showed remnants of low cuboidal or flattened lining cells. The lumens contained bluish or pinkish stringy mucinous material mixed in places with fresh blood. The original diagnosis was pseudomucinous cystadenocarcinoma.

COMMENT

Hypoglycemia.—Two standard oral glucose tolerance tests (50 mg. dextrose) during the period of attacks in case 1 (curves 1 and 2 in the tabulation) showed a slow rise in the blood sugar levels from hypoglycemic to low maximum levels at one and one-half and two hours, respectively, followed by a slow fall to the levels seen in four hours in the second test.

	Curve 1 Mg. per 100 Cc.	Curve 2 Mg. per 100 Cc.
Fasting level	38	75
½ hr.	68	95
1 hr.	72	138
1½ hr.	80	125
2 hr.	120	115
3 hr.	...	90
4 hr.	...	65

Another standard oral tolerance test four months after the attacks had ceased showed a fasting sugar level of 78 mg. per hundred cubic centimeters, which rose to 190 mg. in one-half hour and fell to 65 mg. in three hours—an essentially normal curve. Two epinephrine sensitivity tests during the periods of attack, with 0.5 mg. of epinephrine hydrochloride injected subcutaneously, showed fasting sugar levels of 68 mg. and 70 mg. per hundred cubic centimeters, respectively, with a maximum rise of 10 mg in one-half hour in both tests. Thereafter the levels fell to 65 and 45 mg., respectively, in two hours. Five units of regular insulin, following a fasting sugar level of 70 mg., caused a drop to 60 mg. in one-half hour and 40 mg. in one hour, after which it was necessary to give the patient dextrose intravenously to prevent shock, as he had begun to show premonitory symptoms. Blood sugar levels at intervals while food was withheld showed a slow decrease from 60 mg. per hundred cubic centimeters on arising at 6 a. m. to a low of 40 mg. at 1 p. m., when symptoms appeared. The patient went into shock at 2:20 p. m., when the blood sugar level was 48 mg. Unfortunately, no intravenous dextrose tolerance tests were made.

These tests suggest that during the periods of attack, at least, there was some interference in absorption and probably a low glycogen reserve. The possibility that glycogenolysis was interfered with or that insulin sensitivity increased cannot be excluded. Epinephrine caused only a slight rise in blood sugar, and then a slow response. Insulin in a dose of only 5 units caused a slow but definite decrease in the blood sugar and a sustained response.

Among the various mechanisms that may have produced hypoglycemia in this patient, hepatic insufficiency must be considered in view of the changes in the liver, the abnormal results of liver function tests and the role of the liver in the maintenance of the blood sugar level. However, the exact mechanism is obscure. Seckel [5] reported a case of hypoglycemia in which a large fibroma of the liver was so situated as to exert pressure on the right splanchnic nerves and celiac ganglion, thus presumptively inhibiting sympathetic impulses to the liver. Disruption of sympathetic impulses to the liver has been demonstrated to cause hypoglycemia in cats by Evans, Tsai and Young,[6] and such a mechanism may have been operating in Seckel's case. Since large masses of tumor were present in the region of the celiac ganglion and right splanchnic chain, one might speculate on the possibility of such a mechanism in case 1. However, there was no evidence of inhibition of glycogenolysis in antemortem and postmortem studies of the glycogen content of the liver as reported by Seckel. In case 1 the postmortem analysis of the liver for glycogen was reported to have shown 137 mg. (of glucose) per hundred grams of tissue. Since the necropsy was made nine hours after death, these figures do not help. Conn [7] considers interference with the sympathetic innervation of the pancreas and the adrenal glands to be a mechanism of production of idiopathic hypoglycemia in some cases, and such a mechanism might possibly play a role here also, since the mass of gelatinous material surrounding these organs might easily have interfered with innervation.

It is well known that prolonged oxidation, as in strenuous physical exertion, can lead to hypoglycemic episodes. But it has never been shown that a rapidly growing tumor alone can utilize sufficient oxygen and hence glucose to produce hypoglycemia in the presence of an adequate intake and reserves. Woodward and Fry [8] have shown that the average blood sugar levels in patients with cancer are about 20 mg. higher than those in normal controls on the same hospital diet, and that noncancerous growths also tend to be associated with elevated blood sugar levels. One might logically assume that a rapidly growing neoplasm probably induces increased glycogenolysis and hence some elevation of blood sugar, as long as the glycogen stores or glycogen precursors (fat and protein) are not depleted. On depletion of these stores, however, hypoglycemia might ensue. In the presence of

5. Seckel, H. P. G.: Clin. Investigation **17**:723, 1939.
6. Evans, C. L.; Tsai, C., and Young, F. G.: J. Physiol. **73**:67, 1931.
7. Conn, J. S.: J. A. M. A. **115**:1669, 1940.
8. Woodward, G. E., and Fry, E. G.: Biochem. J. **26**:889, 1932.

possible impairment of absorption, hepatic insufficiency and a wasting disease, the demand for glucose by the tumor might well have led to hypoglycemic blood sugar levels.

Evensen [9] and others have shown that often hypoglycemia develops after gastroenterostomy, and he attributes this to rapid emptying of the stomach with subsequent faulty absorption. Although in case 1 the emptying time of the stomach was not abnormal, there is suggestive evidence of faulty absorption in the deficiency pattern of the small bowel on roentgen examination and the abnormal high fat content of the stool (37 per cent of dry weight) on a low fat diet. The low blood cholesterol (90 mg. per hundred cubic centimeters) and the low serum proteins (4 Gm. per hundred cubic centimeters) could be partially explained on the basis of faulty absorption as well as hepatic insufficiency; certainly loss of protein in the fluid removed by paracenteses played a role. Regardless of the mechanism, the patient was seriously undernourished and, as shown by Gounelle and Marche [10] and others, fatal hypoglycemic shock can develop in undernourished patients with nutritional edemas. Such a mechanism might be all that is needed to explain the present case except that if this were all one might wonder why hypoglycemia is not more often seen in cases of carcinomatosis or other severely debilitating diseases, or in previously studied cases of peritoneal pseudomyxoma.

Other cases in which hypoglycemia was attributed to faulty absorption, as in Frank's,[11] that of a boy suffering from ascariasis (which cleared up on adequate antiparasitic therapy), suggest that at least faulty absorption of glucose may play a role in hypoglycemia. The massive involvement of the mesentery in 2 cases reported here may well have inhibited absorption, even though there was no microscopic evidence of obstruction of the mesenteric lymphatic vessels.

It has been suggested further that the pseudomucin, which contains a polysaccharide conjugated with a protein in the mucoitin-sulfonic acid portion of the complex, may in some manner bind or convert sufficient glucose to result in hypoglycemia when large quantities of pseudomucin are present. (In case 1 the total gelatinous material weighed approximately 9,000 Gm.) This idea may be worth further study.

In the absence of any conclusive evidence establishing the cause of the hypoglycemia, this is best explained as a combination of faulty absorption, hepatic insufficiency and debilitation resulting in sufficient depletion of glycogen, protein and fat stores that the withholding

9. Evensen, O. K.: Acta med. Scandinav. (supp.) **126**:1, 1942.
10. Gounelle, H., and Marche, J.: Occup. Med. **1**:48, 1946.
11. Frank, L. L.: Am. J. Digest. Dis. **11**:195, 1944.

of food precipitated episodes of hypoglycemia. After six weeks of a high protein diet, and after it was no longer necessary to withhold food for any purpose, the attacks ceased. Peripheral edema likewise subsided, although the mass continued to grow. In 2 of the other 3 cases reported here there was likewise a disappearance of the peripheral edema on high protein diets.

DIAGNOSIS OF PERITONEAL PSEUDOMYXOMA

The diagnosis of peritoneal pseudomyxoma was not made clinically in any of these cases. Indeed, in few cases has it ever been so diagnosed. Himmelfarb, Ager, Kozinsky, Peters, Mekhedko and others, as reported by Mekhedko,[12] have, however, made the clinical diagnosis. Mekhedko stressed clinically the indefinite contour of the abdominal masses, the slowly developing enlargement of the abdomen, the absence of cachexia during the greater part of the course and the small fluctuations and lack of change in the percussional note on change of position of the patient, and, finally, a history of recurrent attacks of abdominal pain (presumptive recurrent appendicitis). In addition, the signs and symptoms stressed by Mekhedko, the silent, nonpainful, nature of the swelling early in the course of the disease, the necessity for repeated paracenteses, the engorged abdominal veins and, finally, the terminal symptoms of intestinal obstruction or perforation (in 3 instances) characterized our cases and closely approximate the clinical course described by Krivsky[13] and others.

However, in most cases the diagnosis, if made prior to death, will be made at laparotomy. Yet, despite repeated laparotomies, the nature of the illness was not appreciated in 3 of the 4 cases, being correctly diagnosed at laparotomy only in case 2, and then with assurance only at the second operation. Two factors stand out as being responsible for this failure of diagnosis: 1. The absence of a demonstrable mucocele, the appendix having been surgically removed prior to the onset of symptoms, as in case 3, or the appendix having been buried in the mucinous mass, as in case 1. (It is of interest that at the time of removal of the appendix in case 3 [four years prior to death] it was reported as inflamed.) 2. The reports on biopsy material consistent with colloid or mucogenic adenocarcinoma. Case 2 was recognized as one of pseudomyxoma only when a definite mucocele of the appendix was seen.

The repeated reports of adenocarcinoma are important, for there is no consistent opinion as to the nature of peritoneal pseudomyxoma, and some have thought that both cancerous and noncancerous lesions

12. Mekhedko, V. P.: Vrach. delo. **19**:889, 1947.

13. Krivsky, L. A., Jr.: J. Obst. & Gynaec. Brit. Emp. **28**:204, 1921.

can give rise to the gross anatomic picture. Krivsky [13] reported about 7 per cent to be "malignant" histologically, while Woodruff and McDonald [14] reported 38 per cent to be "malignant." Barzilai [15] expressed the opinion that the disease when of ovarian origin is histologically "benign," although clinically "malignant." Woodruff and McDonald [14] distinguished between "nonmalignant" cystic tumors of the appendix and grade 1 adenocarcinoma of the appendix, which they consider the type of growth of the appendix which may rupture and give rise to peritoneal pseudomyxoma. However, their criterion of cancer of the appendix (lining cells forming pseudoalveoli and invading the underlying stroma) cannot be applied in microscopic examination of peritoneal or omental cystic masses in some cases because, for the most part, the cysts are unlined, or if lined with cells, as in cases 1, 2 and 4, these cells may or may not show such pseudoalveolar or invasive characteristics. In cases 3 and 4 such changes were seen fairly frequently; in cases 1 and 2, very infrequently. Rubnitz and Herman [16] have considered the criteria of cancer to be the presence of lining cells alone, those not lined being considered benign. Such criteria help very little, for many of the cysts will be unlined and others lined, and it is a matter of chance whether the particular section examined will have lining cells. Furthermore, within the same section, the lining may vary from flattened to high cuboidal cells with evidence of goblet formation. The decision as to whether or not the condition is shown to be cancer on histologic observation becomes in such cases almost a matter of individual interpretation, since the obvious evidences of cancer are lacking—mitotic figures, metastases, bizarre cell arrangements, etc.

The important point, therefore, is that even in the presence of cells which may be thought by the examiner to be cancerous a diagnosis of peritoneal pseudomyxoma should be entertained when the history is consistent and laparotomy shows a peritoneum infiltrated with gelatinous cysts, even in the absence of a demonstrable mucocele of the appendix. The finding of a mucocele should expedite matters at once. A cancerous lesion can very likely produce the gross anatomic picture of peritoneal pseudomyxoma, but microscopically, for the most part, the lesions are relatively benign. Even the benign appearance of the cysts, however, in the presence of consistent gross anatomy is not sufficient evidence to warrant a definite diagnosis of peritoneal pseudomyxoma, for I have studied a case of mucogenic adenocarcinoma (presumptively of colonic origin) which was so diagnosed because it had spread or

14. Woodruff, R., and McDonald, J. R.: Surg., Gynec. & Obst. **71**:750, 1940.

15. Barzilai, G.: Atlas of Ovarian Tumors, New York, Grune & Stratton, Inc., 1943.

16. Rubnitz, A. S., and Herman, K. T.: Arch. Path. **36**:297, 1943.

metastasized to inguinal and mediastinal lymph nodes but which otherwise grossly was similar to the 3 cases of pseudomyxoma reported in the foregoing pages, and histologically indistinguishable. However, some of the early authors (Krivsky [13]; Olshausen [8]) might well have considered even that a case of peritoneal pseudomyxoma, for in some of the cases they reviewed the patients did have parenchymal involvement and distant metastases. Furthermore, reports describing peritoneal pseudomyxoma originating from the gallbladder, from persistent patent omphalomesenteric duct and other sites suggest that even the demonstration of a mucocele of the appendix or a cyst of the ovary is not necessary to establish the diagnosis. The important point is, therefore, that the diagnosis is essentially a gross anatomic one, and that to rely on the microscopic changes may often erroneously prohibit a diagnosis of peritoneal pseudomyxoma.

A review of case 4 reveals at least three important points: 1. Because of the original diagnosis of papillary cystadenocarcinoma of the ovary with metastases, no real effort was made for six years to reevaluate the case and attempt therapy. Even though it was suggested on the basis of the large amounts of pseudomucinous-like material obtained at paracenteses that this condition might have had a pseudomucinous origin, the term "carcinoma" had been used and the case was considered hopeless. Then, after six years, in which the patient did not deteriorate, it was finally thought advisable to reattempt surgical treatment. The attempt was successful in completely eradicating the disease. 2. Because the possibility of peritoneal pseudomyxoma of appendical origin was not entertained, even at the time of successful surgical therapy, the appendix was not examined, and eventually it became the source of the patient's death. How in this day and age, after two exploratory laparotomies, this patient escaped an appendectomy, I cannot guess, but she did, and for me it has resulted in a dramatic support of Koerner's theory concerning the origin of peritoneal pseudomyxoma in females. This theory holds that the pseudomyxoma is never the result of a primary pseudomucinous cystadenoma of the ovary but is always secondary to a ruptured mucocele of the appendix. Koerner [4] stated, and is supported by Mekhedko,[12] that a normal appendix has never been reported or demonstrated in a case of peritoneal pseudomyxoma in which the patient was a woman. In at least 25 per cent of reported cases in which the tumor occurred in a woman it had a dual origin imputed to it because in those cases the appendix was examined and a mucocele was found. The lesson to be learned, then, is this: In the presence of a pseudomucinous cystadenoma or cystadenocarcinoma of the ovary with peritoneal implants, one should consider the possibility of peritoneal pseudomyxoma and remove the appendix as well as the tumor, regardless of what the appendix may look like. There is

abundant evidence in the literature, especially the German and Russian, to show that the prolongation of life is greater when both possible sources of the spread of the cystic masses are removed than when the ovary alone is removed. This concept is not stressed in the American literature, and it may well be that a greater awareness of the possibilities will result in greater numbers of surgical cures in cases diagnosed as cystadenocarcinoma of the ovary if the appendix is removed routinely with the ovarian mass, even when there are apparent metastases. Many cases of peritoneal pseudomyxoma must have gone into the records as cases of colloid carcinoma, mucogenic adenocarcinoma, pseudomucinous cystadenoma or adenocarcinoma. Clinically the prolonged course in a case considered hopeless on the basis of pathologic observations and questionable spread or metastases should be the tip-off. Cancers rarely allow a prolongation of life to this extent after spread has occurred, and especially when no treatment, surgical or radiologic, has been attempted. Furthermore, a thorough exploration of the abdomen may reveal that there are no parenchymal metastases, no actual invasions of organs, and this fact should put the surgeon on his guard. The spread of peritoneal pseudomyxoma is entirely along the serous membranes, and if parenchymal involvement occurs, it is rare and probably late in the course. This, then, is a plea for an awareness of the possibility of cure of peritoneal pseudomyxoma as well as a plea to think of it in hopeful terms, and get in early. Do not let a pathologic report scare you out. The disease may be more common than was previously thought, and, indeed, more and more case reports are piling up from year to year.

The importance of arriving at the diagnosis as early as possible must be stressed in light of the fairly numerous reports that life was prolonged by removal of the appendix (and ovary) and as much of the cystic masses as possible (Olshausen,[8] Masson and Hamrick,[17] Timoney,[18] Voight,[19] Meleney [20] and others). Omentopexy has been thought to be of value when it could be performed. Barzilai [15] and Mekhedko [12] both suggested that postoperative irradiation was of some value, and case 4 seems to confirm this opinion.

CONCLUSIONS AND SUMMARY

Four cases of peritoneal pseudomyxoma are reported: In one, hypoglycemia was an incidental finding; in another hypoglycemia reached shock levels; in the third there was massive infarction of the

17. Masson, J. C., and Hamrick, R. A.: Canad. M. A. J. **22**:508, 1930.
18. Timoney, F. X.: Am. J. Surg. **64**:417, 1944.
19. Voight, W. W.: Illinois M. J. **71**:172, 1937.
20. Meleney, T. L.: Surgery **103**:457, 1936.

spleen as a result of compression of the splenic vein and massive encapsulation of the organ with the cystic mucinous growth; the fourth, in which the patient was a woman, was remarkable because of the result obtained with surgical treatment and because death resulted eventually from a perforated mucocele of the appendix.

Various possibilities as to the genesis of the hypoglycemia in 2 cases are discussed. It is felt that the best explanation is that a combination of faulty absorption, hepatic insufficiency and debilitation due to mechanical interference with functions of the bowel and the liver probably led to the hypoglycemic attacks.

The difficulties of diagnosis and the problem of distinguishing peritoneal pseudomyxoma from mucogenic adenocarcinoma are discussed.

It is suggested that more attention be paid to the possibility that in females peritoneal pseudomyxoma may originate in the appendix even in the presence of an ovarian cystadenoma or an ovarian cystadenocarcinoma, and that the appendix be removed in all cases in which the slightest doubt may exist as to the differential diagnosis. Credence is given to the possibility that even in females the appendix and not the ovary may be the site of origin of peritoneal pseudomyxoma.

INFLUENCE OF DICUMAROL® ON STREPTOCOCCIC INFECTION IN RABBITS

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IT HAS been demonstrated chiefly by Menkin [1] that fibrin plays an important part in the localization of infection by forming either a fibrinous network in the tissues or thrombi in the lymphatic channels about areas of inflammation. This hypothesis was first tested by studying the rate at which dyes pass into, and out of, inflamed areas. Observations were also made with various bacteria, and it was noted that in localized infections produced by injecting staphylococci and pneumococci into rabbits fibrin was conspicuous in lymphatic channels, whereas it was less evident or absent after injections of hemolytic streptococci. Because of other factors involved in the localization of infections, such as phagocytosis and the "spreading factor," the explanation based on mechanical fibrin blockage has never been accepted without considerable reservation.

To obtain additional information in this connection, it seemed desirable to study the course of experimental infections in normal as well as in dicumarolized animals in which the mechanism of coagulation would be interfered with so as to prevent or decrease the formation of fibrin. By the utilization of such a method it seemed possible that a more adequate answer to this problem might be obtained.

METHOD

Rabbits weighing from 2,000 to 3,000 Gm. were selected in pairs, so that the treated and control animals in each experiment were approximately of the same weight. The animals were fasted from twenty-four to thirty-six hours prior to, as well as during, the experiment. Water was offered freely. Dicumarol® (3,3′-methylenebis[4-hydroxycoumarin]) was administered orally in gelatin capsules in doses of 6 mg. every other day. Prothrombin time was determined on blood from the ear by the method of Quick. The hair was clipped over one flank, and the rabbit was given an intracutaneous injection of an eighteen hour blood broth culture of hemolytic streptococci (strain H).[2] The culture was diluted in broth

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1. Menkin, V.: Dynamics of Inflammation, New York, The Macmillan Company, 1940.

2. Angevine, D. M.: J. Exper. Med. **64**:131, 1936.

so that an inoculum of 0.1 cc. contained the equivalent of 0.01 to 0.001 cc. of the original culture. The cutaneous lesions of both the control and the treated animals were observed and measured frequently. The measurements represent the average of the two diameters and the height in millimeters. Thus a lesion that measures 40 by 64 by 4 mm. is recorded as 52-4. Those in the table represent measurements made at forty-eight hours except when an animal was killed prior to that time. The prothrombin time was usually determined twice on each animal; the greater response only is included in the table. The blood was cultured at the time of death or when the animals were killed. In the first few experiments the animals were infected on the day following that of the first dose of dicumarol®; subsequently they were infected after 3 doses of dicumarol® had been administered over a period of from three to five days. This permitted a more adequate oppor-

Infections in Normal and Dicumarolized Rabbits

Experiment	Administration of "Dicumarol" and Culture, Day						Cc. of Culture Injected	Prothrombin Time, Sec.	Interval Between Infection and Death	Size of Lesion, Mm.		Blood Culture		Fibrin	
	1	2	3	4	5	6				Treated	Control	Treated	Control	Treated	Control
1	D	I	D	..	D	..	0.01	67	....	52-4	28-6	+ d-4	0	..	..
2	D	I	D	..	D	..	0.01	60	K-10	60-6	24-7	0	0	..	..
3	D	I	D	..	D	..	0.01	120	....	50-8	26-6	+ d-5	+ d-8	..	..
4	D	I	D	..	D	..	0.001	17	K-10	27-6	20-5	0	0	+	+++
5	D	I	D	..	D	..	0.001	60	....	22-3	19-3	+ d-4	0	+	++
6	D	I	D	..	D	..	0.001	180	....	19-4	20-5	+ d 4	0	0	++
7	D	..	D	..	DI	..	0.01	180	K-2	25-3	26-4	0	0	0	+++
8	D	..	D	..	DI	..	0.01	5	K-6	43-4	25-3	0	0	..	..
9	D	..	D	..	DI	..	0.01	180	....	5-1	32-4	+ d-2	0	0	0
10	D	..	D	..	D	I	0.01	35	K-1	35-2	23-4	0	0	+++	+++
11	D	..	D	..	D	I	0.01	180	K-2	90-2	24-3	+	0	0	+
12	D	..	D	..	D	I	0.01	30	K-3	55-3	60-4	0	0	+	+++
13	D	..	D	..	DI	..	0.01	16	K-1	31-3	21-4	0	0	+	+++
14	D	..	D	..	DI	..	0.01	5	K-3	34-3	28-5	0	0	+++	++
15	D	..	D	..	DI	..	0.01	50	K-3	45-3	37-4	+	0	++	+++

D = "dicumarol."
I = injection of culture of hemolytic streptococci (strain H).
K-10 = killed after ten days.
d-4 = died after four days.

tunity for response to the drug. The variations in these relations are indicated in the table.

Histologic preparations were made of the lesions in most of the experiments. In some instances tissue was removed for study at intervals of twenty-four, forty-eight and seventy-two hours from both treated and control animals. In other instances the lesions were removed for sectioning when the animal was killed. The lymph node draining the site of inoculation was also sectioned. To demonstrate fibrin in the tissues, the sections were stained with Mallory's phosphotungstic acid–hematoxylin.

RESULTS

The most important findings are incorporated in the table. Only 2 of 15 treated rabbits (experiments 8 and 14) did not show an increase

of prothrombin time. The response varied widely in different animals (from 16 to 180 seconds). The prothrombin time in normal animals was never more than 5 seconds. The cutaneous lesions of dicumarolized animals were appreciably larger than those of controls (figs. 1 and 2)

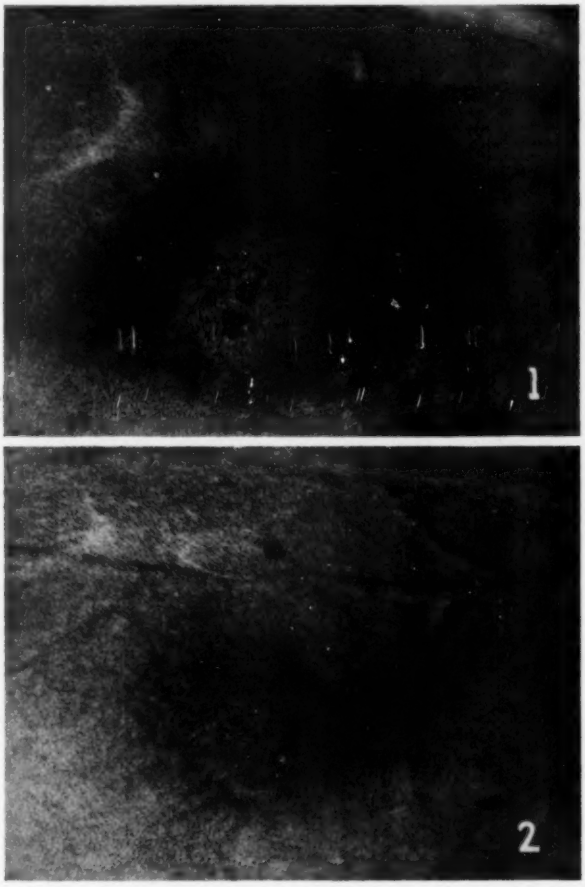

Fig. 1.—Spreading lesion on the skin of a dicumarolized rabbit eight days after an intracutaneous injection of 0.01 cc. of hemolytic streptococcus culture.

Fig. 2.—Localized lesion on the skin of a control rabbit eight days after a similar injection.

in 11 of the 15 experiments (73 per cent). In experiment 9, although the treated animal showed little evident local reaction to the infection, death occurred from bacteremia within forty-eight hours.

Blood cultures were made on all animals. Seven of 13 that responded to the drug with a prolonged prothrombin time had positive cultures, and 5 of them died with bacteremia in from two to five days. In only 1 control did bacteremia develop, and in this animal death occurred after eight days. Histologic sections of skin from both control and treated animals were prepared and stained for fibrin in 11 of the 15 experiments. In 8 of 10 experiments less fibrin was observed in the skin of dicumarolized animals than in comparable untreated controls. No difference was noted in experiment 10. In only 1 instance was more fibrin observed in the skin of a dicumarolized animal (experiment 14); this animal did not respond to the drug, and the prothrombin time was 5 seconds. Fibrin was not observed in the tissues of animals with a prothrombin time of 3 or more minutes. Conversely, significant amounts of fibrin were observed only in animals in which the prothrombin time was only slightly prolonged.

Animals that did not respond to the drug with a prolonged prothrombin time reacted to the infection in a manner similar to the controls. This would tend to eliminate the action of the drug per se as a causative factor.

SUMMARY

Rabbits treated with dicumarol® usually had an increase of prothrombin time. When they were subsequently infected with an intracutaneous injection of a culture of hemolytic streptococci, the infection spread more extensively than in normal rabbits, and 5 of 13 died with bacteremia. Histologic observations indicate that the lack of fibrin in the tissues of the treated animals is probably a factor in the spread of, in contrast to the localization of, infection in the control animals.

Notes and News

William A. Hinton, director of the laboratory of the Boston Dispensary and special consultant of the United States Public Health Service, has been appointed clinical professor of bacteriology and immunology in Harvard Medical School.

Frank M. Townsend, Temple, Texas, is now associate professor of surgical pathology at the University of Texas Medical Branch, Galveston. Dr. Townsend will also be consulting surgical pathologist to the hospitals of the University of Texas.

Howard T. Karsner, former professor of pathology at Western Reserve University, is now adviser to the Surgeon General of the Navy in regard to its medical research program.

The Fifth International Congress of Microbiology will be held Aug. 17-24, 1950, in Rio de Janeiro, Brazil. The secretary of the executive committee is Joaquim Travasses.

After a lapse of five years, owing to the war, the Theobald Smith Award in Medical Sciences, established in 1936 by Eli Lilly and Company, will again be given at the annual meeting of the American Academy of Arts and Sciences. Fellows of the Academy should submit names of proposed recipients to Dr. Gordon K. Moe, University of Michigan Medical School, with full information (in triplicate) concerning the personality, the training and the research work of the applicant. The award will be $1,000 and a bronze medal, given for "demonstrated research in the field of the medical sciences, taking into consideration independence of thought and originality." An additional amount of $150 is available toward traveling expenses. The recipient must be less than 35 years of age on January 1 of the year in which the award is to be made, and a citizen of the United States.

Academic Press, Inc., announces the publication of *Experimental Cell Research*, sponsored by the International Society for Cell Biology. The journal will publish papers dealing with the activity, the structure and the organization of the cell and its subunits, including virus. Technical or theoretic papers on experimental cytologic methods will be included. Papers may be submitted in English, French or German. *Experimental Cell Research* will be edited by Torbjörn Caspersson, Stockholm, Sweden; Honor Fell, Cambridge, England; John Runnström, Stockholm; Francis O. Schmitt, Cambridge, Mass.; Paul Weiss, Chicago; and Ralph W. C. Wyckoff, Bethesda, Md. J. F. Danielli, London, England, will act as editor of communications for the Society. Authors residing in the western hemisphere should send their papers to the editors residing in the United States; those residing in the British Isles should mail theirs to Dr. Honor Fell, Cambridge; papers originating in other countries should be forwarded to the Scandinavian editors. One volume, consisting of four issues, will be published annually.

Books Received

THE CHEMISTRY AND PHYSIOLOGY OF GROWTH. By J. H. Northrop, F. O. Schmitt, K. V. Thimann, K. Volkers, C. B. van Niel, E. S. G. Barron, P. Weiss, J. S. Nicholas, C. P. Rhoads, C. N. H. Long. Edited by Arthur K. Parpart. Cloth. Pp. 293, with illustrations. Price, $4.50. Princeton, N. J.: Princeton University Press, 1949.

The papers were presented at the conference on growth at Princeton University in September 1946.

The subject of growth is one of the most important, if not the most important, considerations in biology. It is therefore a pleasure and a thought-provoking stimulus to find the subject dealt with so admirably in this book by so many outstanding scientists. There is, however, a fundamental question which only one of the contributors considers, and that is—what is growth? One may begin to define growth by calling it a process which spreads before the observer in a display of increasing complexity or of increasing magnitude. But having begun in this way the troubles of definition start. Increasing complexity is obviously differentiation or something akin to it; increasing magnitude is not universally called growth, as witness, take the swelling of cells or gelation processes. Perhaps, as Paul Weiss asseverates in his chapter on "Differential Growth," one cannot study growth but only growing objects. Perhaps, with him, we must find the word to be too ambiguous. And yet most of us, including nine of the ten contributors, intuitively accept the word unhesitatingly as though we understand what it means. We are reluctant to give it up. Having warned the reader that there is this philosophic nut to crack, and there are others, too; he is invited to look at the book.

The book covers the contributions and integrations of ideas from the subjects of physiologic chemistry, bacteriology, embryology, experimental histology and experimental pathology. The synthesis of proteins, cellular metabolism, plant hormones, some nutritional factors and animal hormones go together to make up five of the ten chapters. Under experimental histology is included "Molecular Morphology," as revealed by roentgen ray diffraction and electron microscope technics, and tissue culture studies. Embryologic development taken as representative of "organization," the study of growth rates of bacterial cultures and the results of investigations having to do with experimentally induced neoplasms round out the book.

Of the most direct interest to pathologists is the chapter "Neoplastic Abnormal Growth," by C. P. Rhoads. It would seem to be a fair judgment that in the present state of knowledge one should not expect to find a logically coherent description of the neoplastic process. What is available is a collection of views. These are covered comprehensively with emphasis on hybridization, mammary tumor inciter and the cytoplasmic control of inherited cellular traits. The importance attached to studies of transplantable tumors may be questioned; studies of spontaneous tumor growth are less complicated if more difficult to design. For this reason, research on mammary tumor inciter (milk agent) would appear to promise the most interesting information for doctors of medicine.

The challenging attitude of Paul Weiss in the discussion of "Differential Growth" will alienate a few pathologists, but many of his arguments on the sterility of morphologic studies limited to one environmental condition of the cells are forceful and convincing. This article contains a large portion of speculation and a number of terms not usually associated with the subject. "Modulation" is not a happy choice of a word to describe the cellular morphologic changes which occur in tissue culture and which are reversed by restoring the cells in an intact organism. Since his main theme is the distinction between reversible differentiation (modulation) and irreversible differentiation it would be simpler, if less elegant, to stick to those terms.

The article by C. B. van Niel, "Kinetics of Growth," contains a dissertation on growth curves in the case of micro-organisms and also two ideas which biochemists generally will not agree with. The first exceptional idea is that when large numbers of individuals are involved (as in cultures of micro-organisms), a statistical treatment is superfluous. Whether this claim is justified will depend on what he means by "treatment." Mathematical statistics have been used to great advantage in the theoretic consideration of large numbers and their behavior. While statistical analysis of data may be superfluous, statistical derivation of concepts may be very useful. The second exceptional idea is that "biochemists in particular have come to recognize that the thermodynamic formulations beg the question which has become paramount in today's biochemistry, viz., that of the mechanism whereby the result is achieved." It would seem the wise course, after the extraordinary success of thermodynamics in chemistry, to withhold judgment. Certainly, the studies of in vitro systems described so logically by J. H. Northrop on "The Synthesis of Proteins" and by E. S. G. Barron on "Cellular Metabolism" do not dispense with thermodynamics. The perspective of thermodynamics should be supplementary to the detail and incompleteness of mechanisms.

With respect to the other no less interesting articles the reviewer will point to the "master reaction" in plants proposed by Thimann, will mention the fact that Folkers discusses streptogenin and various derivatives of folic acid in their relationship to growth, and will express his regret that the concept of competitive biologic effects of chemical analogs was practically excluded from the book.

CORRECTION

In the article by Drs. J. H. Cheek and E. E. Muirhead entitled "Bronchial Adenoma Producing an 'Alveolar Cell Carcinoma' Pattern" in the issue of December 1948 (ARCH. PATH. **46**:529, 1948) the legends for figures 3 and 4 should read as follows:

Fig. 3 (case 1).—The so-called "alveolar cell carcinoma" pattern with papilliferous structure from a metastatic nodule of the opposite lung. Lining of alveolar walls with columnar cells of a mucus-secreting type is evident. This pattern was observed not only as a transition from the adenoma but elsewhere in both lungs.

Fig. 4 (case 2).—The glandular, mucus-secreting make-up of the tumor at its center is demonstrated.

On page 532, in the second paragraph under the sidehead "Autopsy," "fig. 3" should be deleted and "fig. 4" should be fig. 3.

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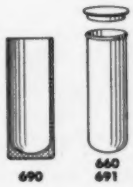

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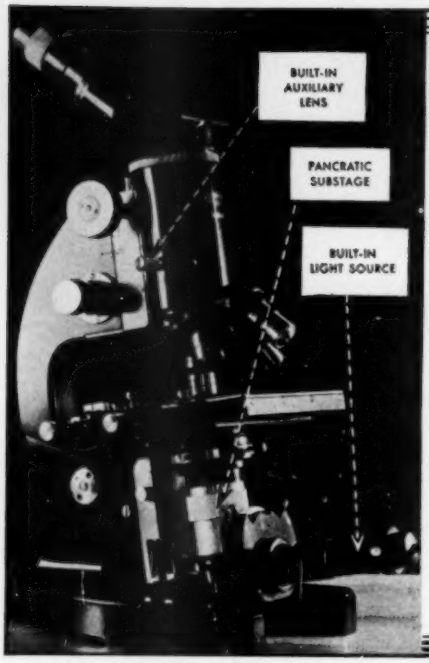

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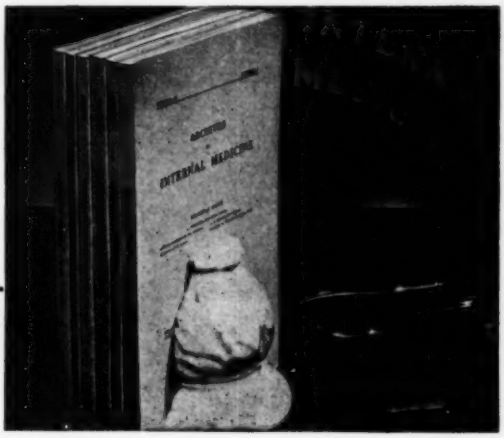

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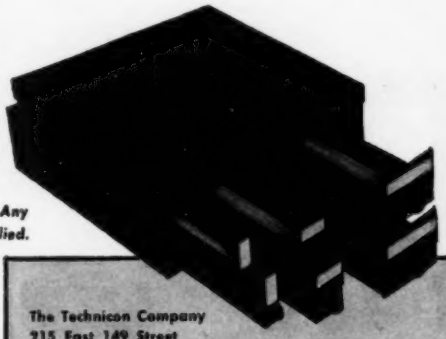

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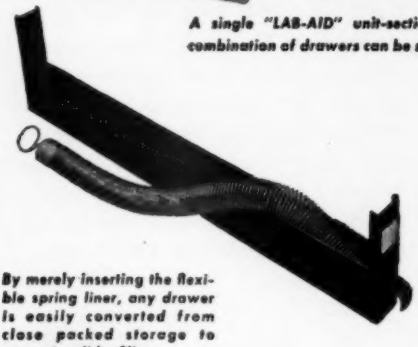

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